ARCHIVES OF SURGERY

VOLUME 48 MAY 1944 NUMBER 5

COPYRIGHT, 1944, BY THE AMERICAN MEDICAL ASSOCIATION

PERMEABILITY OF LYMPH VESSELS AND LYMPH PRESSURE

FERDINAND C. LEE, M.D.

BALTIMORE

The purpose of this article is to present the results of experiments which were intended more to explore new avenues in the physiology of the lymph system than to give intensive study to individual aspects of a limited problem. At this writing it is uncertain when it will be possible to support by a longer series of experiments the conclusions obtained from relatively few pioneering observations.

It has long been known that ligation of the thoracic duct causes deposition of chyle in the retroperitoneal tissues. Whether this condition is due to a rupture of a lymph vessel [1] or whether it represents a transudation through an intact vessel wall [2] has never been decided. The first experiments were planned to shed light on this problem alone, but they soon presented other facets which invited exploration.

EXPERIMENTS

When the chyle-bearing thoracic duct of the cat is ligated in the chest according to a method described in 1922,[3] the resulting deposition of retroperitoneal chyle reaches its maximum in from twenty-four to forty-eight hours. The extent of this chylous effusion is variable, but after maximal effusion the stomach is not covered, certainly never the liver, nor does the mass extend into the pelvis, even though small deposits may be seen along the proximal portion of the iliac vessels. At the end of seventy-two hours much of the extravasated chyle will have been absorbed, and it is rare for any trace of it to remain longer than one hundred and forty-four hours. The deposits in the distal portion of the mesentery, near the intestine itself, are among the first to disappear, whereas proximally the tissue immediately around the intestinal lymph gland is among the last to surrender its chylous deposit. Usually there is a small amount of chylous ascites present by the end of twenty-four hours after ligation of the thoracic duct; however, in another twenty-four hours it is rarely possible to aspirate any more chylous fluid from the peritoneal cavity.

As regards these experiments, the most common site for the first signs of chylous extravasation following ligation of the thoracic duct in the cat was at the inferior border of the cisterna chyli above the pedicle of the left kidney. This observation was made in 7 animals.

In 2 cats the earliest appearance of the retroperitoneal chyle following ligation of the thoracic duct in the chest was in forty-five minutes. For the other 5 animals, the time of appearance was respectively fifty, sixty-five, seventy, seventy-five and eighty minutes. The procedure in the experiments was to open the abdomen thirty minutes after ligation of the duct in the chest, with the animal under intratracheal ether anesthesia, and after inspection of the left cisternal region to close the abdominal incision with towel clips, and to repeat the inspection every five minutes.

Once the retroperitoneal chyle had appeared at the cisterna chyli, it could be found around the intestinal lymph trunks and the mesenteric glands by the end of another fifteen minutes. The subsequent spread of the extravasated chyle in the mesentery toward the intestines became progressively slower.

It may be well to define some of the terms that will be used in the remainder of this article. The mesenteric lymphatics or lymph vessels are situated in the mesentery of the small intestine and conduct the lymph from the small intestine to the intestinal lymph gland situated at the root of the mesentery. This lymph gland is relatively large and conglomerate and should not be confused with the small lymph glands which are frequently found isolated within the mesentery of the small intestine. From the intestinal lymph gland several large lymph vessels, called intestinal lymph trunks, carry the lymph to the

From the Departments of Surgery and Anatomy of the Johns Hopkins University.

1. Cooper, A.: Three Instances of Obstruction of the Thoracic Duct, with Some Experiments Showing the Effects of Tying That Vessel, M. Rec. Private M. A., 1798, p. 86.

2. Schmidt-Mühlheim, A.: Gelangt das verdaute Eiweiss durch den Brustgang in's Blut? Arch. f. Anat. u. Physiol. (Physiol. Abt.), 1877, p. 549.

3. Lee, F. C.: The Establishment of Collateral Circulation Following Ligation of the Thoracic Duct, Bull. Johns Hopkins Hosp. **33**:21, 1922.

cisterna chyli, which in turn discharges its lymph into the thoracic duct.

While the fluid element of the lymph was thus leaving the vessels, the question naturally arose as to the fate of the lymphocytes within the lumens of the lymph channels. The entire trunks of 7 animals were immediately placed in a 4 per cent solution of formaldehyde at the end of the experiment, and subsequently histologic sections

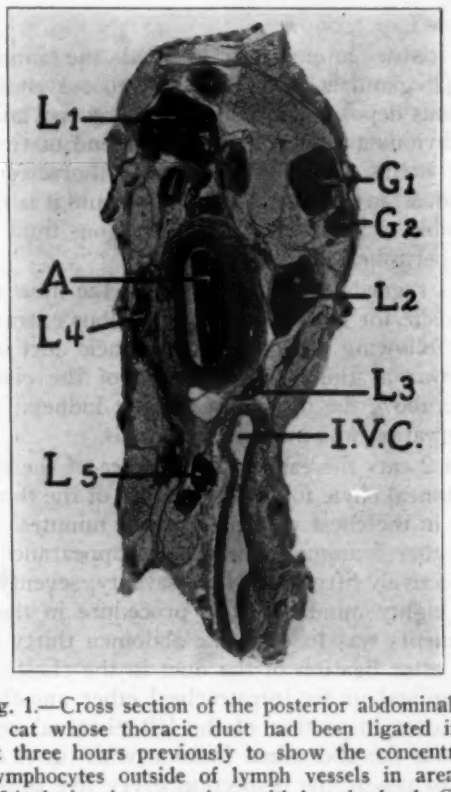


Fig. 1.—Cross section of the posterior abdominal wall of a cat whose thoracic duct had been ligated in the chest three hours previously to show the concentration of lymphocytes outside of lymph vessels in areas *L1* to *L5* inclusive, in comparison with lymph glands *G1* and *G2*. *A*, aorta; *I.V.C.*, inferior vena cava. The area *L1* is shown enlarged in figure 2. Hematoxylin and eosin stain; × 10.

were obtained from various areas, beginning at the point of ligation of the thoracic duct in the chest and continuing down to the lower portion of the abdominal aorta. Blocks were also obtained from the region about the intestinal lymph trunks. All the sections were cut from celloidin-embedded blocks and were stained in hematoxylin and eosin.

It was found that in 5 of the 7 animals the highest concentration of lymphocytes occurred immediately outside of the lymph trunks in the region just above the bifurcation of the aorta. Cephalad to this point the extravascular lymphocytes were progressively less in number, the least number being near the point of ligation of the thoracic duct in the chest. A heavy concentration of these cells was also observed around the intestinal trunks near their entrance into the cisterna chyli. This region, incidentally, had the greatest number of lymphocytes in the 2 other animals in the series. In 1 of these 2 cats the lymphocytes were so heavily masked that they resembled a small lymph nodule (figs. 1 and 2), even though the thoracic duct had been obstructed for only three hours. In another animal the concentration of lymphocytes on both sides of the wall of a lymph vessel was so great that a direct transition seemed to exist (figs. 3 and 4). In the third animal the effect of a twenty-six hour obstruction of the thoracic duct on a lymph gland was shown (figs. 5 and 6). Here the cortex was relatively compact when compared with the edematous medulla with its thin, delicate tissues separated and teased in a fashion which made for better histologic study. Possibly lymphatic obstruction might be used as a means for obtaining finer morphologic details not only of lymph glands but of other organs. The coronary lymph sinus of the lymph gland was small when compared with the extremely large collecting trunks at the hilus.

Fig. 2.—Enlargement of area *L1* in figure 1, to show the irregular packing of lymphocytes outside of a lymph vessel. A few lymphocytes are enmeshed in a fibrin-like network, *F*. A lymph vessel is *L.V.* Hematoxylin and eosin stain; × 70.

Commonly the extensive collections of extravascular lymphocytes are enmeshed in a thin, delicate, lightly eosin-stained meshwork, which resembles fibrin in appearance but is probably

extravasated chyle. This belief is strengthened by the fact that the fluid substance in adjacent chyle-bearing lymph vessels has the same appearance.

Because of the heavy concentration of lymphocytes on each side of the thin wall of a lymph vessel, it was hoped that the actual passage of the lymphocytes through the vessel wall might be studied. Although the preparations were not convincing, the impression was gained from the study of those fields in which the wall of the lymph vessel was cut at a slight angle, so that the endothelial cells were visible as a small plaque, that the lymphocytes passed, if not between, at least through the periphery of, the endothelial cells.

Nor was there a parallelism between the concentration of extravascular lymphocytes and extravasated chyle, because it was common to find the lymphocytes in dense masses, which resembled ribbons, with no chyle present, and on the other hand there were areas with large amounts of chyle which contained only a few lymphocytes. It was not unusual to find small lymph vessels completely packed with lymphocytes, yet rarely was a large vessel more than one-half full of these cells (fig. 3). The areas of heaviest condensation of lymphocytes were not necessarily within the lumens of the lymph vessels but preferably immediately outside of their walls (figs. 2 and 4). Lymphocytes were commonly found on the outside of fat cells (fig. 4) but never within them. Apparently, whatever the factors responsible for the transfer of lymphocytes from their intravascular to their extravascular position may have been—and intravascular pressure may well have been one of them—the effect of these factors was rapidly dissipated once the cells were outside of the walls of the lymph vessels, except for ribbon-like deposits and heavy concentrations (fig. 2), which were not always near large lymph vessels but extended along thin fascial planes. Nor did the lymphocytes escape uniformly and evenly from the lymph vessels (fig. 4).

It will be noted from the preceding description that the concentration of lymphocytes following ligation of the thoracic duct was in tissue essentially proximal to the intestinal lymph gland. What was happening to the lymphocytes in the mesenteric lymphatics immediately distal to the intestinal lymph gland was found from the histologic examination of sections taken from the same animal from which the material shown in figures 3, 4, 5 and 6 was taken and emphasizing the heavy concentration of lymphocytes within and without the lymph vessels. In marked contrast to this heavy deposition, the lymphatics and the tissues just distal to the intestinal lymph gland were entirely normal. The same results were obtained in another animal.

Since lymphocytes, which are of considerable size, can pass through lymph vessels, whose walls are many times thicker than a single endothelial layer, it does not seem unreasonable to believe that chyle can pass through this same type of wall, and probably more easily. The predication of a rupture of the wall is not necessary.

Furthermore, if chyle and lymphocytes can pass readily through the walls of lymph vessels, could also fine particulate matter under similar conditions? To get evidence for this possibility, commercial india ink, sold as Higgins Eternal Black Carbon Writing Ink, was injected centripetally, with the aid of a 10 cc. syringe equipped with a 27 gage needle, into the mesenteric lymphatics of a cat anesthetized with ether. The ink went quickly to a mesenteric lymph gland, which soon became black, but in the meantime the mesenteric lymph vessel which had been receiving the injection no longer had its sharp outline but was becoming blurred, beadlike and fuzzy. As the injection was continued the lymph vessel became indistinct, until it resembled a concatenation of black smudges. Histologic examination of the lymph vessel showed that the

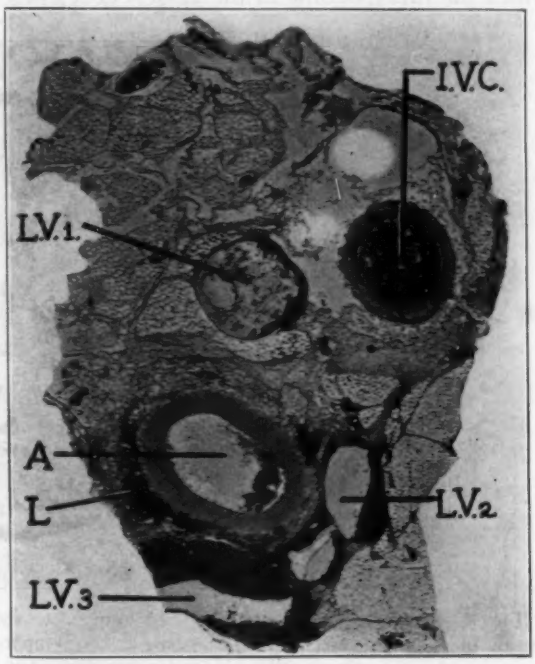


Fig. 3.—Cross section of the posterior abdominal wall of a cat whose thoracic duct had been ligated twenty-six hours before to show the concentration of lymphocytes (black) within the larger lymph vessels, *L.V.1*, *L.V.2* and *L.V.3*, and also at *L* in the adventitia of the aorta, *A*. *I.V.C.*, inferior vena cava. The area *L.V.1* is shown enlarged in figure 4. Hematoxylin and eosin stain; × 13.

ink had gone through the wall of the vessel and had distributed itself in the surrounding, loose areolar tissue. There was no sign of rupture in the wall. This experiment was repeated in 6 animals. In 2 cases the mesentery with its fuzzy lymph vessels was cleared by the Spalteholz method. Examination of such a specimen showed that the particles of ink were in greater concentration immediately outside of the vessel and gradually became more scattered as the distance from the vessel increased. The heavy concentration was not uniform along the vessel but was in waves, more or less evenly spaced.

In fact, in 2 animals it was shown that a direct relationship existed between the amount of pressure of the injected ink and the speed with which the fuzzy outline of the vessels developed.

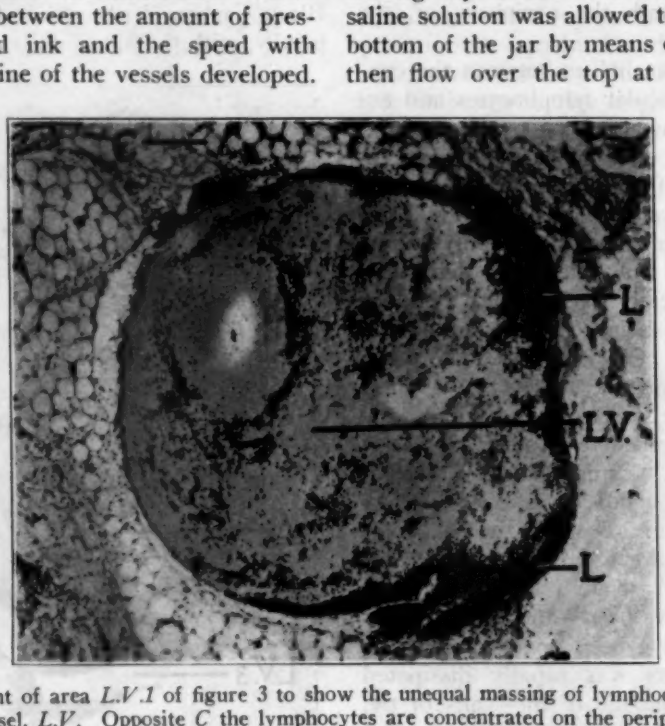


Fig. 4.—Enlargement of area *L.V.1* of figure 3 to show the unequal massing of lymphocytes *L1* and *L2* directly outside of a lymph vessel, *L.V.* Opposite *C* the lymphocytes are concentrated on the periphery of fat cells but are never found inside these cells. Hematoxylin and eosin; × 50.

Thus, for a cat with pressures of 40, 40, 20, 110 and 160 mm. of mercury erected on the injection fluid, the corresponding periods for the appearance of the blurred outline of the vessels, a different lymphatic being used for each injection, were two and a half, three, five, two and three-fourths minutes respectively.

However, it was soon realized that no conclusions regarding the passage of ink particles through the walls of lymph vessels could be drawn from these experiments, because the commercial ink had an ammoniacal odor. Hence the possibility arose that the ammonia may have damaged the walls and thus facilitated the passage of the ink particles.

To eliminate the ammonia factor the ink was dialyzed. After various thicknesses of celloidin and cellophane were tried as dialyzing membranes, to simplify and standardize the procedure the suggestion of Dr. Edgar Poth to use Patapar paper was followed. A sheet of this paper was shaped into the form of a bag, and 200 cc. of the commercial ink mentioned previously was put in it. The neck of the bag was tied with heavy thread, and the bag was allowed to float on the surface of a sodium chloride solution of 0.89 per cent concentration, which filled a brain jar of 1 gallon capacity. The thread around the neck of the bag was then secured to a cross arm, so that this part of the paper bag was prevented from sinking any lower. For seven consecutive days saline solution was allowed to enter slowly at the bottom of the jar by means of a rubber tube and then flow over the top at a rate of 8 gallons (30 liters) per day. In addition, the jar was completely emptied and freshly filled during the first five days. At the end of the week the ink within the paper bag was measured, and the average of three preparations was 230 cc. This showed that the ink had been moderately diluted by the saline solution. The dialyzed ink was kept in a glass-stoppered bottle and served as stock solution.

To test the toxicity of the dialyzed ink, it was slowly injected by means of a syringe into the femoral vein of a cat, which was under light ether anesthesia. Into 1 animal 8 cc. was injected without any apparent harmful results; into another animal 20 cc. was injected, also without causing any ill effects. However, into a third cat 37.5 cc. was injected; this animal seemed well

for one hour later but was found dead the next morning. In none of the 132 experiments covered by this report did any animal receive more than 10 cc. of the dialyzed ink. All reference to ink in the remainder of this article is to the dialyzed ink and not to the stock commercial ink. Furthermore, since the dialyzed ink had about the same specific gravity as the saline solution and since within the limits of the experiment differences between hydrostatic pressures of water and isotonic solution of sodium chloride could not be determined, for the rest of the report such pressures will be given in centimeter columns of water, even though ink was the actual measuring fluid.

Experiments were then undertaken to determine whether the ink particles would leave the lymph vessels the same way that the chyle and the lymphocytes did. In 6 cats the thoracic duct was ligated in the chest with the animal under intratracheal ether or pentobarbital sodium anesthesia, and then after respectively one, one, one and one-third, four, seventeen, and twenty-six hours the mesenteric lymph vessels were injected with ink by means of a 27 gage needle under a hydrostatic injection pressure which varied between 55 and 97 cm. of water. The amount of ink injected varied between 2.6 and 3.2 cc. The injection apparatus was simple and consisted of the barrel of a 10 cc. syringe, acting as a reservoir, to which was attached a rubber tube 3 feet (0.9 meter) long leading to the barrel of a tuberculin syringe, which in turn was equipped with the 27 gage needle. In all cases the ink was found in the same retroperitoneal regions as described previously for the chyle. The ink had a blue color, which increased in depth near the cisterna chyli, thus indicating the probable source of escape.

However, it still remained to be demonstrated whether the ink might not have escaped through a small rupture of a lymph vessel near the cisterna chyli, instead of having permeated the wall of a lymph vessel. To throw light on this point, the trunks of 3 animals described in the preceding paragraph were fixed in solution of formaldehyde, and later the pertinent structures, extending from and including the point of ligation of the thoracic duct in the chest down to the iliac vessels and including the entire lymphatic system from the intestine to the thoracic duct, were removed in one piece and cleared by the Spalteholz method. Subsequently this entire block of tissue was cut transversely with a safety razor blade into thin slices, which were from 2 to 3 mm. thick. These thin preparations were then examined for places where the ink might have left a lymph vessel because of a rupture in the wall. None was found.

Objection might be raised to the high injection pressure of the ink, which was 97 cm. of water in 1 case, so far as this pressure might be relatively excessive and thus simply force the inert particles through the wall of a lymph vessel whose exit was blocked mechanically by a ligature. To meet this criticism ink was first injected into the mesenteric lymph vessels of 3 cats in which there was no obstruction to the thoracic duct. Then the duct was tied, and in all 3 experiments the ink again found its way out of the lymph vessels chiefly at the cisterna chyli. One of these specimens was cleared by the Spalteholz method and examined as described before, and here also no rupture of a lymph vessel to account for the extravasated ink was observed.

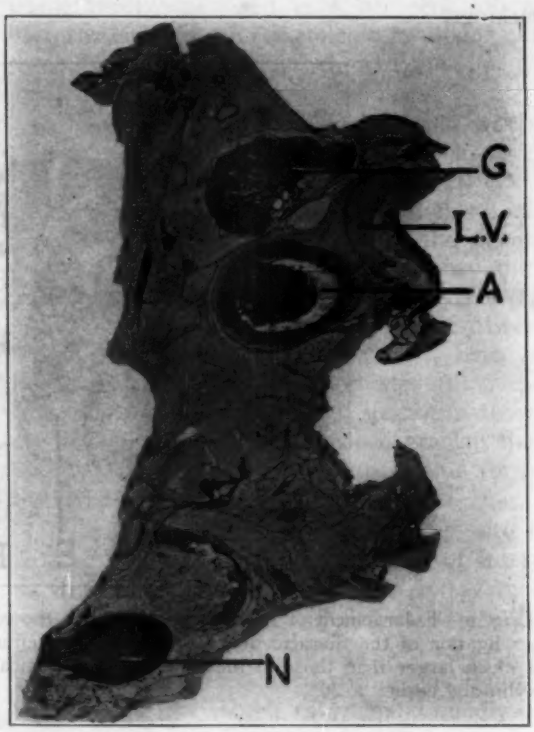


Fig. 5.—Cross section from the same animal as figure 3, to show the relative size and position of the lymph gland, *G*, with reference to the large lymph vessel, *L.V.*, and the aorta, *A*. A sympathetic nerve ganglion is at *N*. The gland, *G*, is enlarged in figure 6. Hematoxylin and eosin; × 6.

If intralymphatic pressure was responsible for the passage of the ink particles, as just mentioned, that pressure must have developed within the peripheral lymph system itself and not from any extraneous source, such as an injection fluid.

In observing a mesenteric lymphatic during its injection with ink under a pressure of 90 cm. of water, it was seen that the vessel first showed

a slight, generalized, uniform enlargement which extended to the intestinal lymph gland. As the injection was continued, the vessel became still larger but revealed points of constriction about 2 to 3 mm. apart, which gave the lymphatic a beaded appearance. The next change, which never occurred until two minutes, and frequently five minutes, after the injection had been started, was the beginning of a blurred outline of the lymph vessel. It was common for this fuzzy appearance to begin in the region of the intestinal lymph gland and not at the point of the injection. If the injection was continued for periods much over five minutes, then the entire perivascular region was covered by a series of ink splotches, which destroyed all markings.

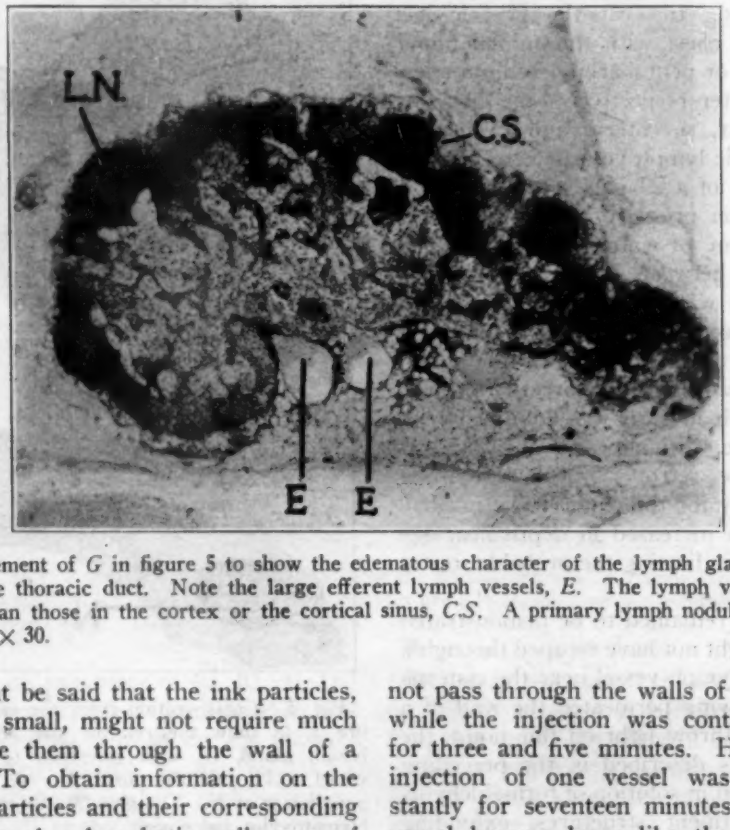


Fig. 6.—Enlargement of *G* in figure 5 to show the edematous character of the lymph gland twenty-six hours after ligation of the thoracic duct. Note the large efferent lymph vessels, *E*. The lymph vessels in the medulla are much larger than those in the cortex or the cortical sinus, *C.S.* A primary lymph nodule is at *L.N.* Hematoxylin and eosin; × 30.

Again, it might be said that the ink particles, being extremely small, might not require much pressure to force them through the wall of a lymph vessel. To obtain information on the size of the ink particles and their corresponding ability to go through a lymphatic wall, some of the ink was centrifuged at 2,200 revolutions per minute for two hours and forty minutes. At the end of this time the specimen looked uniformly black, and from the top of each centrifuge tube 15 cc. of ink was carefully aspirated with the aid of a needle and a syringe. This fraction was supposed to have the smallest particles. The ink remaining in the centrifuge tube was decanted, and at the bottom of the tube was found a small black deposit, which was shaken up in a small amount of saline solution. This fraction was expected to contain the large particles of ink. Measurements of these small and large particles were made with the aid of an oil immersion lens and a micrometer eyepiece, and it was found that the small particles varied up to 1 micron in size, whereas the large particles ranged from 1.2 to 3 microns. Although the dividing band between these two groups was not broad, 4 experiments were carried out to determine whether any difference in their penetration of walls of lymph vessels could be observed.

The first animal had its thoracic duct tied twenty-six hours before, and when the large particles of ink were injected into the mesenteric lymphatics it was found that even with an injection pressure of 70 cm. of water the ink did not pass through the walls of the lymph vessels while the injection was continued respectively for three and five minutes. However, when the injection of one vessel was maintained constantly for seventeen minutes not only did the vessel become large like the other two but a slight blurring of its wall was noted. It is possible that the smaller particles were thus able finally to permeate and go slightly beyond the wall of the lymph vessel.

In the second animal, under the same general conditions, with a pressure again of 70 cm. of water, four injections were made for an interval of three, eight, eight and ten minutes respectively. No blurred outline of lymph vessels was observed. In the third animal, under the same general conditions, it was finally possible to inject one

lymph vessel continuously for ten minutes; no fuzziness occurred.

The last animal in this series was prepared like the previous 3. The injection pressure was, as before, 70 cm. of water. First the large particles were injected into a lymph vessel for five minutes; then the injection apparatus was drained, washed out and filled with ink having the small particles. Two injections of five and eight minutes respectively were made. Then the apparatus was drained, washed out and filled with the ink containing large particles. A single injection for eight minutes was made. Thus the injections of the small particles were flanked by the injections of the large particles. No fuzziness was observed in the outline of any of the vessels. The entire preparation was cleared by the Spalteholz method, and when examined under the Greenough binocular microscope it was seen that fine particles of ink were outside along the course of the lymph vessels which had received the small particles but only within a range of about 2 cm. from the mesenteric lymph gland; no ink particles were seen outside of the vessels filled with the large particles. In these 4 animals pentobarbital sodium was the anesthetic. It was chosen in order to obviate a possible objection to a dilatation which ether as the anesthetic might have given.

It seemed, then, that the size of the particle made a difference in the penetration, and to add to this concept 1 animal, whose thoracic duct was ligated twenty-three hours before, received an injection of a 3 per cent aqueous solution of trypan blue, which consists of particles finer than those of india ink. The injection was made into the mesenteric lymph vessels with syringe and needle without a record of pressure. It was seen at once that the dye diffused through the wall of a lymph vessel twice as quickly as the ink. In another cat the same experiment was repeated except that the injection pressure was 70 cm. of the dye to correspond to the injection pressures used in the experiments mentioned previously. In this case the dye passed through the vessel wall within eight seconds.

In view of the relatively high injection pressures—about 70 cm. of water—the possibility existed that the injection pressure alone might be responsible for the passage of the ink particles through the walls of the lymph vessels in the region of the cisterna chyli following ligation of the thoracic duct, even though the mesenteric lymph gland interposed. Accordingly, it seemed reasonable first to inject the mesenteric lymphatics. Since presumably no obstruction of the lymph vessels existed, the ink would flow into the veins at the termination of the thoracic duct in the base of the neck without any trouble, and the injection pressure would be of little moment. Then the thoracic duct in the chest was to be tied. From this time on the pressure in the inferior part of the thoracic duct would build up of itself, and if any ink escaped from the lymph vessels it would be due to this pressure and not to the initial injection pressure. In the first animal, under pentobarbital sodium anesthesia, 8 cc. of the ink was injected into the mesenteric lymphatics with syringe and needle in twenty minutes. The abdomen was closed, and the thoracic duct was ligated in the chest. Thirty-five minutes later the abdomen was again opened, and a bluish discoloration, obviously ink, was found in the left renal region. The whole trunk was fixed in 4 per cent solution of formaldehyde, and histologic sections taken through the cisterna chyli showed that ink was outside of the lymph vessels.

In the second animal, 2.5 cc. of ink was injected into the mesenteric lymphatics in seventeen minutes at a fixed pressure of 70 cm. of water. The thoracic duct was ligated nine minutes later, and the region of the cisterna chyli on the left side was observed thirty minutes subsequently, when a questionable faint bluish discoloration was noted. However, twenty minutes later the color was definitely blue, and fifteen minutes later the color was still deeper. Examination of the cleared specimen showed the ink distributed in the loose areolar tissue about the cisterna chyli. There was no rupture of the lymph vessels.

Since the experiments were leading into the field of lymph pressures, it seemed of interest to determine what some of the intravascular lymph pressures were. On gross inspection, when a cat's mesenteric lymph vessel was opened with a needle or sectioned with a quick snip of the scissors, the lymph rolled out limpidly and gave no evidence of spurting as if under pressure. The pressure, then, in these vessels must be low. To measure it, the same simple apparatus as described before was used. The mesenteric lymphatics were filled with ink; the barrel of the 10 cc. syringe, serving as a reservoir, was attached to an arm which could be moved up and down on a stand, so that different pressures of ink could be obtained.

To measure the pressure in the mesenteric lymphatics with this apparatus, the level of the ink in the reservoir was placed about 3 cm. above the level of the vessel into which the injection was to be made. At this low pressure ink would roll out of the needle slowly, but when the point of the needle was bathed in the warm saline solution with which the assistant constantly

irrigated the preparation the ink would flow more freely and would obscure the lymph vessel to be injected were it not for this frequent washing. Once the point of the needle had entered the lymph vessel, the ink particles could be seen on the bevel of the needle, and as the reservoir was raised a level was reached at which the ink would leave the point of the needle and slowly continue its flow into the lymph stream. At this moment, with the aid of calipers, the height of the level of the ink in the reservoir above the point of the needle was measured. This measurement was considered to be the pressure within the mesenteric lymph vessel, and from a series of 8 animals the pressure was found to be respectively 3.0, 4.0, 5.3, 5.3, 5.9, 6.0, 6.7 and 6.8 cm. of water, the average being 5.2 cm. of water.

In animals with a large amount of fat in the mesentery, not only was it difficult to enter a lymph vessel but because a certain depth of fat had to be pierced to reach it the point of the needle was frequently blocked, and higher readings were obtained. Lean animals always gave better preparations.

The preceding figures represent the end pressure within the mesenteric lymph vessel proximal to the site where the point of the needle came to rest when it was directed, as always, toward the intestinal lymph gland. Because the shaft of the needle near its point completely filled the distal segment of the lymph vessel and thus prevented lymph from passing along the outside of the needle, these figures do not represent side pressures. It is doubtful whether there is much difference between the side pressure and the end pressure as determined by the method just described. Possibly the figures given are a little low, since the direction of the flow of lymph is away from the point of the needle; however, the amount and the rate of flow must of necessity be very small. Any one having access to the fine glass capillary needles used to determine intracapillary blood pressure could easily determine the side pressure in the mesenteric lymph vessels. Apparently this type of equipment was used by Königes and Otto [4] in 1937 when they found that the pressure within the lymphatic of an intestinal villus of a cat, anesthetized with dial, was 33.3 cm. of water. The steep gradient of this figure to 5.2 cm. of water, which is the average of the values obtained for the mesenteric lymph pressures, is striking.

It is not the purpose of this paper to explain this difference or to enter into a discussion of the forces responsible for the production of lymph. Enough evidence has not accumulated to make such a correlation possible. However, according to Königes and Otto the hydrostatic pressure within the central lymphatic of a villus of the small intestine of a cat is 33.3 cm. of water, and the capillary blood pressure in a neighboring villus is 42.6 cm. of water. What apparently is not known is the tissue pressure for the villus. The nearest approximation, probably, to this value is that for the subcutaneous tissue of man as obtained by Wells, Youmans and Miller,[5] and it is about 7 cm. of water.

Objection may properly be made to the use of this figure for tissue pressure in the villus, and yet, even though there is some fundamental histologic similarity in the two areas, the tissue pressure in the villus could be 21 cm. of water and still not invalidate the conclusion that obviously lymph is not going to collect in a lymph capillary when the hydrostatic pressure within that capillary is 33.3 cm. of water and the pressure in the surrounding tissue is only 7 or even 21 cm. of water. Osmotic pressure must make up the difference. To obtain this osmotic pressure, proteins must be present in the lymph capillary in a higher concentration than in the fluid of adjacent tissue. But Drinker and Yoffey [6] stated that lymph and tissue fluid are approximately identical; therefore, there can be no material difference in the osmotic pressure of these two fluids. If Königes and Otto are correct, then there must be a high concentration of proteins in the lymph capillaries, with a gradual reduction as the lymph reaches central and larger lymph vessels, from which collection of the fluid is simple and for which chemical analyses have shown that the protein content is relatively low (Drinker and Yoffey). That there might be such a difference in protein content for various lymph vessels is a new physiologic concept for this vascular system. On the other hand, if subsequent work supports that of Drinker and his associates, the figure of 33.3 cm. of water for the hydrostatic pressure in a lymph capillary as determined by Königes and Otto is too high. But since these two authors used the same technic for measuring pressures in capillaries as they did for determinations on blood capillaries and obtained values for the pressure in blood capillaries which

4. Königes, H. G., and Otto, M.: Studies on the Filtration Mechanism of the Intestinal Lymph and on the Action of Acetylcholine on It and on the Circulation of the Intestinal Villi, Quart. J. Exper. Physiol. **26**:319, 1937.

5. Wells, H. S.; Youmans, J. B., and Miller, D. G., Jr.: Tissue Pressure (Intracutaneous, Subcutaneous and Intramuscular) as Related to Venous Pressure, Capillary Filtration, and Other Factors, J. Clin. Investigation **17**:489, 1938.

6. Drinker, C. K., and Yoffey, J. M.: Lymphatics, Lymph and Lymphoid Tissue, Cambridge, Mass., Harvard University Press, 1941.

agree in general with those of other investigators, one naturally turns reluctantly to the technical method as a source of error, particularly since this method has been widely adopted. Before any conclusions can be drawn, three determinations are required: first, of the tissue pressure in the villus; second, of the protein content of the central lymph capillary of the villus, and, third, of the protein content of the fluid giving rise to the tissue pressure. For the present it would seem that the value of the pressure in a lymph capillary as determined by Königes and Otto is too high.

To return to the consideration of the gradient of the pressure from 33.3 cm. of water in the central lymph capillary of the villus to 5.2 cm. of water in the mesenteric lymphatic, it is possible but not probable that an extremely small lymph gland or even lymph follicles intercalated between these two areas might account for the extensive difference. But that a large lymph gland, such as the intestinal lymph gland at the root of the mesentery in a cat, might act as a pressure buffer was shown by the following experiments.

The problem was to find out whether ligation of the thoracic duct in the chest would cause sufficient back pressure to increase the pressure in a mesenteric lymph vessel.

In the first cat, the pressure in the mesenteric lymph vessels was measured one and two-thirds hours after ligation of the thoracic duct. The pressure in six successive lymphatics was 3.2 cm. of water. In the second animal, under ether anesthesia also but two and two-thirds hours after ligation, the pressure was 5.8 cm. of water. The third animal, four and one-sixth hours after ligation, showed a pressure of 3.2 cm. of water in each of six different vessels. For the 3 remaining animals of this series, the interval between the ligation and the taking of pressure was respectively twenty-five and three-fourths, twenty-six, and twenty and one-half hours; the corresponding pressures were 6.0, 5.5 and 5.7 cm. of water. It is thus apparent that ligation of the thoracic duct had little effect on the pressure of a mesenteric lymph vessel, particularly when compared with an average of 5.2 cm. of water in animals mentioned previously who had had no previous ligation of the thoracic duct.

But the relationships between the pressure at the point of ligation of the thoracic duct and that in the intestinal lymph gland still were unknown. Previous work, in 1923,[7] had shown that lymph pressure was gradually built up behind the thoracic duct when it was obstructed in the base of the neck. That this pressure might be considerable even in the intestinal lymph trunks was accidentally discovered in a cat whose thoracic duct had been ligated an hour and a half before. A snip with scissors of an intestinal trunk sent up a sudden spurt of lymph to a height which was estimated to be about 15 cm. That such a pressure was present in what seemed to be only a moderately distended lymph vessel was not suspected.

To determine what the ordinary pressure in the mesenteric lymph vessels was as compared with that in the intestinal trunks, for 3 animals under pentobarbital sodium anesthesia the following respective values expressed in centimeters of water were obtained: 3.0 and 0.5; 5.3 and 1.3; 6.7 and 1.0. Obviously, the intestinal lymph gland acted as a pressure buffer. In this respect one can only speculate that the normal function of a lymph gland is to prevent a sudden flood of lymph from passing suddenly into a reservoir, like the cisterna chyli. These receptacles may be unable to pass the lymph along as fast as it is received, and thus build up pressure and force the lymph to permeate the walls of the lymph vessels and to collect in the perivascular spaces and, by implication also, in the peritoneum or other mesothelial-lined spaces. With the lymph gland standing as a guard under normal conditions, adjustments of volume and pressure of the lymph may be established in the periphery. Even in disease, such as inflammation, the lymph gland may be able to adjust much greater degrees of lymph pressure and volume.

However, with the thoracic duct tied in the chest, the pressure relationships were opposite to those given in the preceding paragraph. In 4 cats in which the duct had been tied respectively two and two-thirds, four, twenty-six, and twenty-six and one-half hours before, the corresponding pressures of a mesenteric lymph vessel and an intestinal lymph trunk were respectively: 5.8 and 21.1; 3.2 and 16.5; 5.5 and 30.0; 5.7 and 63.5 cm. of water.

These measurements showed that ligation of the thoracic duct did not increase the pressure in the mesenteric lymph vessels but did raise the pressure in the intestinal trunks. It should be noted that in the last 3 of the 4 animals just mentioned the pressure within the intestinal lymph trunks was measured by inserting an 18 gage needle attached to a glass tube having a millimeter bore. The height to which the lymph rose in the tube was considered to indicate the lymph pressure of the side wall, since the needle did not obturate the lumen of the vessel. Because the walls of the intestinal lymph trunks were

7. Lee, F. C.: Some Observations on Lymph Pressure, Am. J. Physiol. **67**:498, 1923-1924.

thin and since even slight manipulation of the needle would enlarge the opening of the wall to a greater size than that obstructed by the needle, thus causing a leak and producing a low pressure reading, the shaft of the needle near the point was coated heavily with petrolatum in order to seal the leak around the needle.

That such a high lymph pressure as 63.5 cm. of water could be developed is not surprising in view of the pressure of 120 cm. which Field, Drinker and White [8] obtained in the leg of a dog above the site of a sterile inflammation. In all probability the valves in the lymph vessels, in addition to the structure of the intestinal lymph gland, were responsible for the gradient of pressure, which was normal in the mesenteric lymph vessels. Of these two factors, it is believed that the lymph gland played the larger role, because both pressure readings were taken near the gland, which eliminated the consideration of many valves. Besides, the edematous character of the medulla of the lymph gland, as shown in figure 6, indicated that the valves in the efferent vessels were not competent.

The fact that the intestinal lymph gland acted as a barrier between the high pressures built up in the intestinal trunks and the low pressures in the mesenteric lymphatics following ligation of the thoracic duct may indicate that the pressure was probably the chief factor responsible for the extravasation of lymphocytes, as mentioned earlier in this report.

It may be well to point out that since small particles may pass through the wall of a lymph vessel, particularly when the pressure within the vessel is high, the condition of lymphangitis may be due to an inflammatory reaction around bacteria situated within the wall of the lymph vessel or immediately outside of it.

Again, since certain portions of a lymph vessel, such as the segment immediately distal to the intestinal lymph gland, seem to be more permeable than other sections, it is possible that such a weakness may be responsible for the formation of lymph cysts.[9]

There still remained the consideration of whether the intestinal lymph gland would act as a buffer should the pressure in the mesenteric lymph glands be raised. Ordinarily it might be expected that the lymph node would not impede an excessive flow of lymph which is moving in its normal channels and in the normal direction. And if the volume of lymph were increased, would the proximal portion of the lymph gland allow it to pass as fast as it was presented or would the lymph stream be impeded and pressure built up on the distal side of the gland?

To throw some light on this problem, an increased flow of lymph from the small intestine was obtained by injecting 0.2 cc. of turpentine with a 27 gage needle into the antimesenteric serosa every inch (2.5 cm.) for 10 inches (25 cm.) of a cat's small intestine in the direction of normal peristalsis after the pressure of a control mesenteric lymph vessel just proximal to the injected segment had been taken. Pressure readings were then observed in the successive mesenteric lymphatics which drained the segment of the bowel which had been treated with turpentine. In the first animal, this pressure increased from 6.6 cm. to 40.5 cm. of water by the end of seventeen minutes, successive distal vessels for each determination being used. After five more minutes, the same reading of 40.5 cm. was obtained. By this time the mesenteric lymph vessels were larger and fuller, indicating an increase in the amount of lymph. At this point the pressure of an intestinal trunk was measured. The reading was 11.5 cm. of water, indicating a distinct difference in pressure between the two sides of the lymph gland.

The second cat was pregnant, weighed 4 Kg. and showed a gradual rise of pressure in a mesenteric lymph vessel from 5.9 cm. to 23.7 cm. of water by the end of one and one-third hours. Fourteen minutes after this highest reading had been taken, the pressure had fallen to 13.6 cm. of water. At this point the lymph pressure in an intestinal trunk was 4.1 cm. of water.

In the third animal, the pressure in a mesenteric lymph vessel increased from 6.0 cm. to 23.6 cm. of water at the end of fifty-seven minutes, at which time, with the pressure still going up, the pressure of an intestinal lymph trunk was 14.6 cm. of water.

The observations on 3 animals showed that the intestinal lymph gland would buffer volumes and pressures of lymph flowing in the normal direction, but not as effectively as when it was flowing in the reverse direction. Probably the valves of the lymph vessels might account for some of this difference. In addition, small amounts of turpentine possibly were carried along in the lymph stream and reached the lymph gland, causing enough irritation to produce, even in such a relatively short time, some obstruction to the lymph channels, which accounted for a difference in pressure.

That the lymph gland, in view of the pressure relations just described, is in any way comparable

8. Field, M. E.; Drinker, C. K., and White, J. C.: Lymph Pressure in Sterile Inflammation, J. Exper. Med. **56**:363, 1932.

9. Lee, F. C.: Large Retroperitoneal Chylous Cyst, Arch. Surg. **44**:61 (Jan.) 1942.

to the possible buffer action of the blood vessel rete mirabile, which cushions the central nervous system of whales (cetacea), is purely speculative.

A few general remarks about the experiments may now be made.

At first the anesthetic used was intratracheally administered ether. But when the possibility arose that this anesthetic might be partly responsible for the permeability of lymph vessels, pentobarbital sodium was employed intraperitoneally, in a dose of 0.7 cc. of a 5 per cent aqueous solution per kilogram of body weight. Even the thoracic duct in the chest was ligated with the animal under general pentobarbital anesthesia. However, it was soon felt that there was little difference in the action of the two anesthetics as far as these experiments were concerned, and the majority of the animals received pentobarbital, ether being given only when the thoracic duct was ligated in the chest. No experiments were made to determine whether the pentobarbital sodium administered intraperitoneally had any direct effect on the lymph vessels.

Great help was derived from the use of a small loupe, which was worn like a pair of spectacles and which gave a magnification of about three diameters. It was used for every injection.

The animals were kept warm by means of an electric light, which was placed near the structure under examination. Frequent washing with warm saline solution prevented drying of the tissues.

Whenever it was desired to have the mesenteric lymphatic system filled with chyle, the cat was starved for twenty-four hours and then fed rich milk at least three, preferably four, hours before the anesthetic was given. Meat as a substitute for the milk was unsatisfactory because it increased the time required for the formation of chyle.

SUMMARY

In experiments on cats it was found that ligation of the thoracic duct in the chest produced an extravasation of chyle, first in the region of the cisterna chyli, as early as forty-five minutes after the operation. From this general region the chyle spread retroperitoneally and also into the leaves of the mesentery. Small lymph glands became edematous.

Under these conditions, the lymphocytes were concentrated in the lymph vessels distal to the ligation of the thoracic duct but not beyond the intestinal lymph gland, which acted as a barrier. In addition, a large number of lymphocytes passed through the walls of the lymph vessels and were frequently deposited in masses resembling lymph glands. The greatest concentration of the lymphocytes was in the region immediately below the renal veins. It is probable that intralymphatic pressure played a part in forcing the lymphocytes into this extravascular position.

Commercial india ink when injected into the mesenteric lymphatics soon passed through the walls of these vessels without causing a rupture. When this ink was used after having been dialyzed against saline solution, permeation did not occur so readily.

When the thoracic duct was ligated first, the dialyzed ink passed through the lymph vessels, like chyle and lymphocytes, without requiring a rupture of the walls.

It was found that the large particles of centrifuged, dialyzed ink were held back by the walls of the lymph vessels, whereas the small particles passed through. Trypan blue, containing still smaller particles, went through more readily.

Pressure within the mesenteric lymph vessels was found to be about 5.2 cm. of water; in the intestinal lymph trunks, about 1.0 cm. of water.

Ligation of the thoracic duct in the chest caused no appreciable increase in the pressure in the mesenteric lymph vessels, but it did cause the pressure in the intestinal lymph trunks to rise to as much as 63.5 cm. in 1 instance. The large intestinal lymph gland seemed to act as a buffer in the lymphatic system.

This gland also acted as a buffer when the pressure in the mesenteric lymph vessels went as high as 40.5 cm. of water while that in the intestinal trunks registered only 11.5 cm.

ADMINISTRATION OF SUCCINYLSULFATHIAZOLE BEFORE AND AFTER HEMORRHOIDECTOMY

LIEUTENANT LEO L. LEVERIDGE
MEDICAL CORPS, ARMY OF THE UNITED STATES

Hemorrhoidectomy is an elective operative procedure, traditionally performed in a contaminated field. The presence of large numbers of potentially pathogenic bacteria in this operative site, and flowing over the healing wounds postoperatively, has always had to be accepted as unavoidable. With recent developments of chemotherapy, means appear now within reach to alter these conditions.

Two drugs, sulfanilylguanidine and succinylsulfathiazole,[1] have been reported to decrease the bacterial flora in the gastrointestinal tract, apparently without excessive systemic absorption. The newer drug, succinylsulfathiazole,[2] appears to be less toxic and yet to be as effective as sulfanilylguanidine, with the additional advantage of being effectual in the presence of ulcerating lesions of the bowel.[3]

This study was made possible by the cooperation of the following officers of the Medical Corps of the Army of the United States on the staff of the Station Hospital, Camp Blanding, Fla.: Major J. V. Freeman, Chief of the Surgical Service; Major J. E. Ryan, Chief of Septic Surgery, and Major J. T. Cuttino, Chief of the Laboratory Service. The problem was suggested by Major J. W. Annis, Chief of the Gastrointestinal Section of the Medical Service, and the work could not have been done without the assistance of Major A. Fodor, Sanitary Corps, Army of the United States, Assistant to the Chief of the Laboratory Service.

Dr. E. J. Poth, Galveston, Tex., and Dr. E. L. Burbidge, Sharp and Dohme, Philadelphia, made many helpful suggestions.

1. The succinylsulfathiazole (sulfasuxidine) employed in this study was furnished by Sharp & Dohme, Philadelphia.

2. Miller, E.; Rock, H. J., and Moore, M. L.: Substituted Sulfanilamides: N^4-Acyl Derivatives, J. Am. Chem. Soc. **61**:1198, 1939. Moore, M. L., and Miller, C. S.: Dicarboxylic Acid Derivatives of Sulfonamides, ibid. **64**:1572, 1942.

CHEMISTRY OF SUCCINYLSULFATHIAZOLE

Structurally, succinylsulfathiazole is a succinic acid derivative of sulfathiazole. It is relatively strongly acid in reaction. Its solubility in water is low, 0.070 Gm. dissolving in 100 cc. of water at 37 C. However, the sodium salt of succinylsulfathiazole is considerably more soluble; as much as 50 Gm. can be dissolved in 100 cc. of water.

TOXIC REACTIONS TO SUCCINYLSULFATHIAZOLE

Toxic manifestations of succinylsulfathiazole reportedly are "infrequent and mild. . . . An occasional individual may complain of dizziness, headache, or loss of appetite."[4] There have been recorded, however, 2 instances of severe reaction. In 1, which was the only instance of such reaction among a total of 250 patients receiving the drug, the patient had a prompt recovery;[4] in the other, an isolated case, the patient succumbed to a fatal agranulocytosis.[5] Both patients were noted to have headache, nausea and vomiting, and chills and fever. Each of the 2 manifested a reaction to plain sulfathiazole as well as to the succinylsulfathiazole. It may be postulated that these patients were hypersensitive to sulfathiazole, which is reported to be liberated from succinylsulfathiazole by hydrolysis in the intestines and the liver.[3]

3. (*a*) Poth, E. J.; Knotts, F. L.; Lee, J. T., and Inui, F.: Bacteriostatic Properties of Sulfanilamide and Some of Its Derivatives: I. Succinylsulfathiazole, a New Chemotherapeutic Agent Locally Active in the Gastrointestinal Tract, Arch. Surg. **44**:187 (Feb.) 1942. (*b*) Poth, E. J., and Knotts, F. L.: Clinical Use of Succinylsulfathiazole, ibid. **44**:208 (Feb.) 1942.

4. Poth, E. J.: Succinylsulfathiazole: An Adjuvant in Surgery of the Large Bowel, J. A. M. A. **120**:265 (Sept. 26) 1942.

5. Johnson, S. A. M.: Acute Agranulocytosis Due to the Administration of Succinylsulfathiazole, J. A. M. A. **122**:668 (July 3) 1943.

BACTERIOLOGIC STUDIES OF SUCCINYLSULFATHIAZOLE

E. J. Poth and his associates have made the original basic study of succinylsulfathiazole.[3] They have shown the drug to be almost totally lacking in antibacterial activity in vitro against Escherichia coli but in vivo to decrease the coliform bacteria count from about 10,000,000 to less than 1,000 organisms per gram of wet stool in one to seven days (usually in three to five days) of oral administration.

In addition to Esch. coli, they observed that the Shiga, Flexner and Sonne strains of the dysentery bacillus were especially susceptible to the antibacterial action of this compound. The specific action of succinylsulfathiazole on the dysentery bacillus (Flexner) has been confirmed.[6] Apparently other organisms in the intestines were affected by succinylsulfathiazole given orally, although these were not identified.

It was reported [4] that the gram-positive and the gram-negative organisms, which are normally equal in number, decreased under succinylsulfathiazole therapy at approximately the same logarithmic rate for a few days, until the gram-positive population became constant. The number of gram-negative bacteria continued to fall, and this decrease was said to be due not solely to the change in coliform organisms.

The drug was said to have no apparent effect on the growth of the typhoid and paratyphoid organisms, Streptococcus faecalis alpha or Bacillus proteus. Also, Aerobacter aerogenes was considered more resistant than Esch. coli to the action of succinylsulfathiazole.[3b]

With succinylsulfathiazole therapy the stools became soft, gelatinous, mucoid, paler and relatively odorless, contained visible undigested food particles and were smaller in bulk.

REPORTED APPLICATIONS OF SUCCINYLSULFATHIAZOLE IN SURGICAL PRACTICE

It was reported that at laparotomy following preoperative preparation with succinylsulfathiazole the bowel was found to be collapsed and free from gas and fecal material. The mucosa showed no evidence of local irritation due to action of the drug. In an experiment, the colon of a dog receiving this therapy was divided transversely through one third of its diameter, and the lesion was observed to heal without the production of fatal peritonitis, provided that the bowel was found empty at the time of laparotomy.[3b]

A series of 50 patients undergoing surgical treatment of the large bowel who were given the drug as preoperative preparation and as postoperative therapy were observed to have an unusually smooth postoperative course. Serious complications due to infection following fecal contamination were not encountered, and shortened periods of hospitalization and of convalescence were reported.[4]

PRESENT STUDY

It was decided to study a small, controlled series of patients subjected to hemorrhoidectomy to whom succinylsulfathiazole was given preoperatively and postoperatively in order to determine whether this drug promised to alter the usual postoperative course.

All patients with uncomplicated hemorrhoids admitted to the station hospital, Camp Blanding, Fla., for surgical treatment during a seven week period were included in this study. As the patients were admitted, all but 1 were alternately placed in the group receiving succinylsulfathiazole or in the control group. Cooperation was voluntary on the part of the soldiers, and only 1 patient declined to take the drug. He was placed in the control group. Twenty patients were followed—10 controls and 10 receiving the drug. The average age of the men in each group was found to be 26 years.

Succinylsulfathiazole was given on the basis of 0.5 Gm. per kilogram of body weight for the first twenty-four hours, followed by a maintenance dose of 0.25 Gm. per kilogram daily, divided into six portions, to be taken every four hours. This was administered between five and nine days preoperatively, the average period being six and six-tenths days, and for twelve to fourteen days postoperatively. A smaller dose (0.1 Gm. per kilogram daily) may be equally effective for maintenance after the coliform bacillus count of the stools has decreased to 1,000 organisms per gram or lower.[7] It was felt, however, that until the smaller dose has been generally accepted, in this new use of succinylsulfathiazole it was wiser to give the drug in amounts which had already been established as effective.

Patients receiving succinylsulfathiazole had complete blood counts and a urinalysis every other day. Levels of the sulfonamide drug in the blood were determined daily for the first few days and then about every third day. Coliform bacteria counts of the stools were fol-

6. Smyth, C. J.; Finkelstein, M. B.; Gould, S. E.; Koppa, T. M., and Leeder, F. S.: Acute Bacillary Dysentery (Flexner): Treatment with Sulfaguanidine and Succinylsulfathiazole, J. A. M. A. **121**:1325 (April 24) 1943.

7. Burbidge, E. L., Sharp & Dohme Medical Research Division: Personal communication to the author.

lowed. For comparison, two or three complete blood counts were taken for each of the control patients.

The controls were prepared with magnesium sulfate administered orally and a cleansing enema the night before operation, whereas both of these were omitted in the preparation of patients receiving succinylsulfathiazole. (These patients at no time were given any laxatives, enemas or liquid petrolatum, which are said to impede the action of the drug.[3]) At operation, feces were rarely encountered in the rectum and were found no more frequently in one group than in the other.

Preoperative diet and sedation were identical for the two groups.

OPERATIVE PROCEDURE

Hemorrhoidectomy was performed by anatomic dissection (modified Milligan-Morgan procedure). No sutures were employed to approximate the cut mucocutaneous edges. This operation was particularly adapted to this study because it left large areas denuded of mucosa and skin. Hence the rapidity of healing and regeneration was easily observed, and the effect, if any, of the drug was most readily assessed.

Under spinal anesthesia, the patient was placed in the prone position, and the area about the anus was cleaned with alcohol and was sprayed with either merthiolate solution or another suitable antiseptic. The patient was draped, and the anus was gently dilated with one to three fingers. The hemorrhoids were identified, and they were successively removed as follows:

An Allis clamp was placed on an external hemorrhoid and another on the skin, about 1 inch (2.5 cm.) distal to the hemorrhoid and in a line with it to serve as guide. The corresponding internal hemorrhoid was clamped near its base with the tip of a curved Kelly clamp. A suture-ligature was tied about the base of the hemorrhoid, and the excess length of the suture was retained for later use. Then commencing ½ inch (1.2 cm.) distal to the external hemorrhoid, an incision was made along each side of the hemorrhoid and continued as far as practicable in the mucosa toward the suture-ligature. By a combination of sharp and of blunt dissection, the hemorrhoid was separated from its bed. In so doing, the integrity of the sphincters was maintained. When the dissection had proceeded to within ⅝ inch (1.4 cm.) of the suture-ligature, one end of this suture was carried on a needle once through the cut edges of the mucosa, tied and then tied around the entire stump of the hemorrhoid. The mass distal to the ligature was cut off. Hemostasis of the hemorrhoidal bed was obtained by pressure and, when it was found necessary, by additional ligatures, varying in number from one to three. Few were found necessary.

The same procedure was repeated on the remaining hemorrhoids, and care was taken to leave bridges of ¼ inch (0.6 cm.) to ½ inch (1.2 cm.) of intact skin and mucosa between dissected areas. Any external hemorrhoidal tissue remaining was excised or was punctured by undermining the mucocutaneous bridges. No. 1 plain catgut (Curity brand or a comparable size of other manufacture) was employed throughout. A gauze pack lubricated with 1 per cent nupercaine hydrochloride ointment was inserted into the rectum, and a pressure bandage was applied externally. In cases 7 and 9, sulfathiazole ointment (1 per cent) was employed on the pack as a lubricant. It was also applied externally during the postoperative period in these 2 cases.

Postoperative care was identical for the two groups, except for the previously mentioned laboratory procedures in the case of the patients given succinylsulfathiazole. Also, the control patients received liquid petrolatum, as has been indicated, whereas it was not given to those receiving the drug.

All patients were examined practically every day. They reported the number and the character of their bowel movements and the degree of associated tenderness. Excessive bleeding was noted, as well as loss of appetite and nausea or vomiting. They were inspected for external edema and for evidence of healing in the rather large wounds of the perianal skin. Starting with the seventh postoperative day, digital and anoscopic examinations were made every other day. Tenderness, healing and congestion of the anorectal skin and mucosa were thus evaluated.

TOXIC MANIFESTATIONS

No toxic symptoms were manifested while succinylsulfathiazole was administered preoperatively. The following were observed on the first and succeeding postoperative days:

Loss of appetite was noted in 7 patients of the 10 receiving succinylsulfathiazole for an average of three days' duration. Of the controls, 5 had the same complaint for an average of two days.

Nausea was felt by 7 of the patients receiving the medication for an average of two days, as compared with 3 control patients who were nauseated for one day each.

Vomiting was observed in 3 patients given the drug, as compared with 1 control. All of these had this symptom for one day, except 1 patient receiving succinylsulfathiazole, who vomited on two days.

Since the control group differed from that receiving therapy only in the frequency and the duration of the postoperative complaints just mentioned, it is questionable whether these can be considered true toxic symptoms. They may represent aggravation, by the large volume of medication administered, of a slight functional gastrointestinal irritability associated with this operation. In the last 3 cases the method of administration of the drug by means of 0.5 Gm. capsules was changed by dissolving the doses of succinylsulfathiazole in peppermint water alkalinized with sodium bicarbonate. Approximately the same rate of "toxic" symptoms was noted in

these 3 patients as in the preceding 7 who received capsules.

In the first patient given succinylsulfathiazole (case 1), undue alarm was caused by loss of appetite and by moderately severe nausea and vomiting on the first postoperative day. The drug was then discontinued. The reaction of this patient, therefore, could not be considered in the postoperative evaluation of the drug, although he was observed with the others.

The level of sulfonamide compound in the blood, free and combined, was repeatedly less than 2 mg. per hundred cubic centimeters of blood in all cases. Crystals of the compound were never found in the urine.

Significant changes were noted in the blood picture only for patient 3, in whom granulocytopenia and anemia developed. This patient had a history of bruising easily. There was no history of previous sulfonamide therapy. On the eighth postoperative day, after receiving the drug fifteen days, he suddenly manifested a white blood cell count of 4,700 with 40 per cent polymorphonuclears and 55 per cent lymphocytes. The red blood cell count was 3,300,000 and the hemoglobin content 76 per cent (Hellige). The blood counts improved in the next four days; so use of the drug was not discontinued. Then on the twelfth postoperative day, after nineteen days of therapy, another low count was obtained—white blood cells 4,100, with 41 per cent polymorphonuclears and 58 per cent lymphocytes, red blood cells 3,900,000, with 70 per cent hemoglobin. Administration

*Results Observed**

	Controls										Patients Receiving Succinylsulfathiazole									
Case Number	2	4	6	8	10	12	14	16	18	20	1	3	5	7	9	11	15	17	19	21
Age of Patient	31	32	21	26	28	27	23	19	35	21	24	27	37	23	31	29	18	23	32	23
Total dose of drug in grams	..	..	..	..	..	..	..	..	..	..	110†	420‡	327	378	419	299	327	348	450	453
Maintenance dose per Kg. of body weight	..	..	..	..	..	..	..	..	..	..	0.26	0.25	0.25	0.26	0.24	0.26	0.25	0.25	0.25	0.25
Days of preoperative therapy	..	..	..	..	..	..	..	..	..	..	5	7	5	7	7	6	6	7	7	9
Number of hemorrhoids excised	3	3	4	3	4	3	4	4	4	3	3	3	3	3	3	5	3	3	3	3
Postoperative days before first bowel movement	1	3	3	4	2	3	2	2	2	1	1	2	1	3	1	1	2	1	2	2
Average number of postoperative bowel movements daily	1	1	2	1	3	1	1	1	2	2	1	2	1	1	2	2	1	1	1	1
Days of severe rectal pain	1	1	1	1	2	1	3	1	0	0	1	0	2	1	1	0	0	0	1	1
Days of severe tenderness on bowel movement	6	8	14	9	2	4	3	3	5	0	5	8	0	6	5	0	4	0	9	4
Days of discernible anal edema	5	3	6	11	13	11	7	12	7	2	13	3	3	12	8	>12	5	8	14	9
Days of moderate tenderness on digital examination	>17	>14	>16	>11	>13	>13	>16	10	9	0	>14	9	>12	>13	>15	12	7	7	>17	>12
Days of moderate congestion of mucosa	17	>14	>16	>11	13	13	>16	>14	>10	13	9	30	12	0	13	12	10	>13	>17	>14
Days to near-healing externally	17	12	8	>11	11	14	14	15	9	>13	14	21	11	13	15	11	>12	>13	13	12
Days to near-healing internally	17	>14	16	11	13	13	12	12	10	13	14	30	12	9	13	12	10	11	>15	9
Postoperative days to discharge	18	15	17	12	14	15	17	16	15	14	15	55	13	15	16	13	13	13	18	14

* > indicates that symptom was still present or that near-healing was not yet attained on the patient's discharge from the hospital.

† Administration of the drug was discontinued on the first postoperative day.

‡ Granulocytopenia and anemia developed.

of succinylsulfathiazole was discontinued on this day. The following day an equally low blood count was reported. The counts increased spontaneously thereafter, but abnormally low readings were again obtained on the nineteenth, twentieth, thirty-first and thirty-sixth postoperative days, with low normal counts in the interim. On the twenty-fifth postoperative day the patient was given liver extract (50 U. S. P. units at first and then 20 units intramuscularly every other day for several weeks). Finally the blood count became stable. From the fiftieth to the sixtieth postoperative day it averaged white cells 6,200, with 50 per cent polymorphonuclears and 44 per cent lymphocytes, red cells 3,700,000 and hemoglobin 75 per cent. When questioned, the patient complained of some lassitude and some anal burning due to a persistent postoperative anal fissure. At the time this is written, the fissure appears to be healing, and in all other respects the man is well and active.

RESULTS

The results are summarized in the table.

Four of the 10 patients given succinylsulfathiazole had no severe postoperative pain; 2 of the same number of controls likewise had no severe pain.

Three patients receiving the drug did not have marked tenderness associated with defecation postoperatively, as compared with 1 control.

Marked perianal edema was present in 2 patients receiving succinylsulfathiazole, 1 of whom displayed this reaction for four days and the other for one day. This degree of edema was observed in 5 of the control patients, in 1 for two days and in the others for one day each. The duration of perianal edema, when recorded as the least discernible cutaneous distention present, averaged about eight postoperative days for each group.

Evaluation of the postoperative course in terms of tenderness to digital examination, of external and internal healing and of congestion of the anus and rectum cannot be expressed statistically because many patients were discharged before complete relief of all of these symptoms was reached. Consideration of the figures, however, confirms the clinical impression that there was no appreciable difference in the rate of healing or in the resolution of inflammation in the two groups.

One patient receiving succinylsulfathiazole (case 17) had a fairly severe postoperative hemorrhage, which was readily controlled by repacking. None of the controls bled to any extent. As an occasional hemorrhage will be encountered after this procedure, 1 instance is not significant.

With the exception of patients 1 and 3, who did not have the full course of therapy, the patients receiving the drug were discharged to full duty in an average of fourteen days postoperatively. The controls were discharged in fifteen days' average time.

COMMENT

After hemorrhoidectomies, the individual variation of postoperative course is great. To prove a statistically valid difference between any 2 groups of patients subjected to hemorrhoidectomy would require studies of at least several hundred persons. Nevertheless, if succinylsulfathiazole therapy is of great practical value for such patients it should have been apparent in this small controlled group. Although the figures reported appear to indicate a somewhat more comfortable average postoperative course when succinylsulfathiazole is used, the series is too small for these figures to be statistically significant. In any case, the results are not striking, nor do they appear to justify the use with minor surgical procedures of a drug such as this, with toxic potentialities.

These results are probably due to the fact that succinylsulfathiazole is ineffectual against certain of the organisms present in the stool. On the other hand, even if a drug were available which would eliminate all potentially pathogenic intestinal organisms, it is possible that the natural resistance to infection of wounds in the anorectal region is so great that production of a sterile field would not hasten their healing.

SUMMARY AND CONCLUSIONS

Succinylsulfathiazole has been reported by other physicians to be the drug of choice for the treatment of bacillary dysentery and for use before and after surgical operations on the large bowel.

A trial series of 20 patients were subjected to hemorrhoidectomy, 10 receiving the standard dose of succinylsulfathiazole and 10 being controls.

This series included 1 patient who manifested a mild, asymptomatic, transitory, recurrent granulocytopenia and anemia after fifteen days of therapy.

It is concluded that the use of succinylsulfathiazole as preoperative and postoperative therapy in hemorrhoidectomy does not promise to be sufficiently advantageous to justify the risk of its occasional toxic manifestations.

CORRECTION

In the article by Dr. Robert R. Linton entitled "Two-Stage Operation for Carcinoma of the Transverse Colon Producing Duodenocolic Fistula: Report of Two Cases," which appeared in the March issue (ARCH. SURG. **48**:197, 1944), credit for the first successful extirpation of the head of the pancreas for carcinoma of the head of the pancreas was given to Dr. Whipple, whereas it should have been given to Dr. Alexander Brunschwig, who published the first report of a case in which this operation was used (*Surg., Gynec. & Obst.* **65**:681, 1937).

TRAUMATIC RETROPERITONEAL RUPTURE OF THE DUODENUM

PRESENTATION OF A CASE AND REVIEW OF LITERATURE

LIEUTENANT (jg) MURRAY L. JOHNSON (MC), U.S.N.R.

Traumatic surgery at the present time is of great interest to physicians. Traumatic retroperitoneal rupture of the duodenum, though rare, is a condition well worth attention. Reports show plainly that too frequently operation is delayed and that the lesion may be missed at operation, and that the prognosis is poor because of these factors. Thus it behooves every surgeon who is called on to treat patients as surgical emergencies to have some established knowledge of duodenal ruptures into the retroperitoneal tissues and to be able to find an occult lesion when exploring the peritoneal cavity. He will be helped by knowledge of technical factors gained from reports of successful or unsuccessful cases.

Reports [1] from the present conflict have recorded cases of intestinal rupture from "immersion blast force." Study of these reveals the mechanics of many of the retroperitoneal duodenal injuries. Experimental and physical data suggest that intestinal rupture caused by immersion blasts is due not to the first impulse of the blast but more likely to the secondary pressure and concussion effect of actual movement of water away from the scene of underwater explosion. These forces have been reported as acting up to a distance of several hundred feet. There are also undoubted cases of rupture due to crushing of the duodenum against the vertebral column. Many authors have felt that a crushing force was responsible for a majority of intestinal ruptures; but with reports of rupture by blast force this mechanism becomes important, particularly in the duodenum where almost its entirety is in a protected area. Also the pathologic findings are those to be expected when a "blow-out" occurs—no contusion of the duodenal wall, the mucosal edges not injured, and the location of the retroperitoneal rupture of the duodenum most frequently away from the vertebral column. Concomitant injury of the pancreas is rare, and this would not be so if most of the injuries resulted from crushing by direct force. The forces reported to produce retroperitoneal rupture of the duodenum are usually a sudden blunt blow to the abdomen, as the kick of an animal, not necessarily over the duodenum, and sudden squeezing, as when a person is caught between two vehicles, or falls from moderate heights.

The force necessary to rupture a normal bowel is surprisingly low. Andrews [2] found that a force of 6 to 10 pounds (2.7 to 4.5 Kg.) will rupture the intestine in man. Since the pylorus is at one end of the duodenum and the superior mesenteric artery and root of the mesentery press on the fixed duodenojejunal flexure at the other end, producing a closed system, with proper direction of opposing forces rupture will occur.

Retroperitoneal rupture of the duodenum frequently occurs alone, though of course it may be associated with other serious conditions. In the case I report there was an isolated lesion, producing a clearcut clinical picture, as I did not see the patient until twenty hours after the rupture occurred. The case may well be presented in some detail as a pure case of retroperitoneal rupture of the duodenum due to trauma.

REPORT OF CASE

N. W., a 10 year old boy, was admitted to the hospital at 4: 10 p. m. on Jan. 23, 1943, complaining of severe pain in his abdomen, right loin and back. The history revealed that at 8: 30 p. m. the previous evening the patient had been struck by an automobile while riding his bicycle. His wind was knocked out, but he soon recovered. He was taken to a local physician, who

---

From the surgical services of Union Memorial Hospital, Baltimore, and U. S. Naval Hospital, Charleston, S. C.

This article has been released for publication by the Division of Publications of the Bureau of Medicine and Surgery of the United States Navy. The opinions and views set forth are those of the author and are not to be construed as reflecting the policies of the Navy Department.

1. Breden, N. P.; d'Abreu, A. L., and King, D. P.: Sudden Compression Injuries of the Abdomen at Sea, Brit. M. J. **1**:144-146 (Jan. 31) 1942. McMullin, J. J. A.; Palma, J.; Pugh, H. L.; Gates, R.; Ecklund, A. M., and Hamlin, H.: Symposium on Immersion Blast Injuries, U. S. Nav. M. Bull. **41**:1-32 (Jan.) 1943. Greaves, F. C.; Draeger, R. H.; Brines, O. A.; Shaver, J. S., and Corey, E. L.: An Experimental Study of Underwater Concussion, ibid. **41**:339-353 (March) 1943. Friedell, M. T., and Ecklund, A. M.: Experimental Immersion Blast Injury, ibid. **41**:353-363 (March) 1943. Friedell, M. T., and Burke, R.: Report on the Causation of Blast Injury, ibid. **41**:363-366 (March) 1943.

2. Andrews, E. W.: Pneumatic Rupture of the Intestine, a New Type of Industrial Accident, Surg. Gynec. & Obst. **12**:63-72 (Jan.) 1911.

examined him and advised him to return if he did not improve. That night the right side of the abdomen and back became progressively more tender, and he vomited whenever he attempted to take water; there was no blood in the vomitus, however. He had a normal movement of the bowels the following morning, and voiding of urine was essentially normal. Another local physician seen in the morning advised hospitalization. It was after 4:00 p. m. when he was brought into the city and hospitalized. The past history was otherwise unimportant.

He was a well developed and well nourished boy with a flushed face. He was lying quietly. There was some grunting with respiration, and apparently he was in considerable distress. His temperature was 102 F. (rectal), the pulse rate 120, respiration 32 and blood pressure 105 systolic and 65 diastolic. His abdomen was slightly distended with generalized spasm, being more rigid on the right side. The points of greatest tenderness were the right costovertebral angle, flank and upper right quadrant of the abdomen. Rebound pain was not as intense as pain on pressure. Liver dulness was normal. The most striking auscultatory phenomenon was the clear transmission of the cardiac sounds over the entire right side of the abdomen (Claybrook's sign). A few borborygmi were heard. There was a small area of ecchymosis slightly to the left of the umbilicus. The leukocytes numbered 14,200, polymorphonuclear forms predominating; hemoglobin was 89 per cent. Urinalysis gave normal results except for a trace of albumin and numerous pus cells with clumps. (Two specimens were examined. There had been no previous urinary trouble.) A roentgenogram of the abdomen with the patient in the upright position showed "no evidence of air in the peritoneal cavity and the intestines were normal." There was no evidence of emphysema of the tissues in the roentgenograms.

Under brief observation, he did not seem to improve. At 10 p. m., twenty-five and one-half hours after injury, with the patient under ether anesthesia, laparotomy was performed, an upper right rectus incision being utilized. A small amount of straw-colored fluid was present in the peritoneal cavity. The large bowel was distended with gas. The entire large and small bowel, stomach and urinary bladder were examined before a small area of edema and yellowish discoloration of the parietal peritoneum just lateral to the flexion of the duodenum was investigated. No gas was present in these tissues. A small amount of fibrin extended into the peritoneal cavity. The peritoneum was opened and explored with the forefinger, the lesion being easily found on the lower lateral curve of the posterior part of the duodenum. This was mobilized by dividing the reflection of the peritoneum and rolling the duodenum forward, exposing an everted hole about 3 to 4 cm. in diameter. The edge of the intestine looked healthy. The ampulla of Vater was palpated about 3 cm. away. There were several small areas of fat necrosis and the entire retroperitoneal bed was a yellowish, edematous, homogeneous mass. There was no evidence of injury to the pancreas. The rupture was closed with a Connell inverting suture of zero chromic catgut, reenforced with one row of mattress sutures of fine black silk. The resulting lumen was adequate and the duodenum was allowed to fall back in place. A small muscle-splitting incision was made down to the peritoneum in the right flank for drainage, and since there was a diffuse edematous infiltration of the entire retroperitoneal area, one cigaret drain was inserted down toward the pelvis and one up to the lower pole of the kidney. One intraperitoneal cigaret drain was inserted through a lateral stab wound down to the duodenum along the under surface of the liver. The appendix presented itself and was removed, the stump being tied and inverted. Closure of the abdominal incision was accomplished with chromic catgut and silk skin sutures, 5 Gm. of crystalline sulfanilamide being incorporated in the peritoneal cavity and incision. The patient received 500 cc. of dextrose solution and 250 cc. of plasma on the operating table, and his condition remained good throughout. A nasal stomach tube was inserted, and the patient was returned to the ward. The operating time was one hour and twenty minutes.

His general condition progressively improved. Cyanosis, apparently from the sulfanilamide placed in the wound at operation, developed almost immediately and lasted for thirty-six hours. Sodium sulfathiazole, 2 Gm. twice a day, was given for prophylaxis until the fourth day, when administration of oral doses of 1 Gm. of sulfathiazole every four hours was begun. With the stomach tube in place, water was given as desired from the day of operation. On January 27 (fifth day) the stomach tube was removed and hourly feedings of 1 ounce (30 cc.) of broth alternating with albumin water were started, the amount being increased gradually. On January 29 the patient was put on clear liquid diet, and by February 2, on a regular low residue diet. On January 20 (seventh day) the skin sutures were removed and the drains loosened, and on January 31 all drains were removed. On February 1 a small abscess of the wound was opened, yielding cultures of Staphylococcus albus, Escherichia coli and beta hemolytic streptococcus. This healed rapidly. Discharge became profuse from the extraperitoneal drainage incision on February 2 (eleventh day). The drainage, though purulent and creamy, was sterile on both aerobic and anaerobic cultures. Carmine given by mouth on February 3 did not come through the drain and there was no evidence of bile (ruling out duodenal fistula); so it was assumed that the discharge consisted of liquefied products of the digestive ferments in the large retroperitoneal area. On February 4 a sulfathaizole rash appeared, the drug was stopped and the temperature, which had been 100 to 102.4 F. (rectal) since operation, came down to normal.

Fluoroscopy on February 8 revealed no evidence of the duodenal lesion, and there was free passage of barium down the intestine.

The patient was discharged from the surgical service on February 25, thirty-three days after admission.

On March 4, he was readmitted with fever, leukocytosis and tenderness of the right flank. A residual thick-walled retroperitoneal abscess was drained through the posterior part of the flank. Recovery was uneventful.

COMMENT ON CASE

This case illustrates points brought out in other cases reported during the last half century. In the first place, retroperitoneal rupture of the duodenum occurs with little evidence of external trauma, and the signs of generalized peritonitis do not exist; thus operation may well be delayed unless the syndrome of exquisite tenderness in the costovertebral angle with spreading symptoms leads one to think of the duodenum. The patient is obviously ill, but is not in shock. In the case reported the numerous white cells in the urine I believe were due to the irritation of the intestinal ferments surrounding the kidney and ureter; this has been true in

other cases. At operation the fibrin and the yellow retroperitoneal edema over the lateral curve of the duodenum were indications for further exploration. Proper mobilization of the duodenum was essential to proper identification and closure of the rupture. Regarding drains, the area obviously needing most drainage was the entire right retroperitoneal space; this was done extraperitoneally. Drainage lasted several weeks, a sterile foul creamy pus beginning to exude about seven days after operation. The fact that the patient returned after discharge for drainage of a residual abscess indicates my undue optimism that a single stab wound could drain the entire retroperitoneal space; his return could have been avoided by an additional retroperitoneal drain near the tip of the twelfth rib.

In addition, the contaminated peritoneum overlay an injured duodenum, and a subhepatic drain appeared to be indicated. Pus drained for only one day, the eighth day; then the wound closed promptly. Just how much good the sulfa drugs did is hard to say, but at twenty-six hours, the contaminated area was bacterially as well as chemically soiled. The fact that the condition of the patient was at no time critical and that his improvement was progressive makes me feel optimistic regarding the therapeutic possibilities even when operation is unfortunately delayed.

REVIEW OF THE LITERATURE

Obviously, statistics are made up largely of reports of individual cases, and reports of fatal cases are less likely to appear in print than are those of cases in which treatment was successful. Therefore, I shall confine the presented facts to those that will help in recognizing and treating this condition.

Regarding the incidence of ruptured duodenum, Rowlands [3] in 1923 compiled 381 cases, published and unpublished, of rupture of the intestine, including 23 of the duodenum, 157 of the jejunum, 158 of the ileum and 43 of the colon.

Schumacher,[4] in 1910, and Miller,[5] in 1916, wrote excellent articles reviewing the subject of retroperitoneal rupture of the duodenum. Schumacher collected 91 cases of rupture of the duodenum caused by blunt force, of which 24 were retroperitoneal, and Miller collected 22 additional cases of retroperitoneal ruptures. Of these 46 patients, 37 were operated on and only 5 survived, a mortality of 89 per cent. In 14 of the 37 patients operated on, the lesion was not found. As Miller states, "The large proportion of cases in which the rupture was missed at operation is particularly striking when one remembers that the cases were in the hands of thoroughly trained abdominal surgeons."

Furtwaengler [6] presented an interesting paper in 1922 discussing late manifestations of retroperitoneal duodenal ruptures, reviewing several cases in which the diagnosis was not reached until duodenal fistulas developed, as late as two months after the original injury. Two of his cases were reviewed, one by Schumacher and the other by Miller. He compiled 118 cases of rupture of the duodenum (anterior or posterior location not specified), in 14 of which, or 11.9 per cent, the patient was cured.

These late manifestations may in truth be due to delayed perforations, the various stages of which have been reported. Meiner,[7] in 1932, reported a case of retroperitoneal laceration of the duodenum in which no perforation occurred; the patient recovered. Only the outer coats of the duodenum were torn. In Betto's [8] case, in 1938, a retroperitoneal hematoma was found at operation, about two and one-half hours after injury. Apparently the duodenum was not thoroughly inspected; however, there was no leakage of bile or gas at this time, which would correspond to an incomplete rupture of the duodenum. The area of hematoma was packed with iodoform gauze, and Betto reports that on removal of the gauze on the eighth day drainage of bile and gas began. These manifestations of a duodenal fistula persisted for ten days before the perforation closed spontaneously. Thus one may assume that perforation of an injured duodenum may occur at least several days after trauma, and that bizarre cases, as reported by Furtwaengler, may result when perforation finally occurs in a previously traumatized area.

Leibowicz [9] in 1930, stated that he had reviewed the literature of duodenal rupture up to that time and that 177 cases of traumatic rupture of all types had been reported. However, no adequate listing or bibliography is presented.

3. Rowlands, R. P.: Subcutaneous Rupture of Intestine, Brit. M. J. **1**:716-717 (April 28) 1923.

4. Schumacher, E. D.: Surgery of the Duodenum, Beitr. z. klin. Chir. **71**:482-527, 1910.

5. Miller, R. T.: Retroperitoneal Rupture of Duodenum by Blunt Force, Ann. Surg. **64**:550-578 (Nov.) 1916.

6. Furtwaengler, A.: Late Perforation of the Duodenum After Contusion, Deutsche Ztschr. f. Chir. **175**:261-291, 1922.

7. Meiner, E.: Retroperitoneal Injuries of the Duodenum, Schweiz. med. Wchnschr. **62**:761 (Aug. 13) 1932.

8. Betto, O.: Traumatic Contusion and Rupture of the Duodenum, with Report of a Case, Riv. di chir. **4**:116-127 (March) 1938.

9. Leibowicz, M.: Subcutaneous Injuries of Duodenum, Zentralbl. f. Chir. **58**:2205-2206 (Aug. 29) 1931.

TABLE 1.—*Cases of Retroperitoneal Rupture of the Duodenum in World Literature Up to May 1943 Exclusive of Those Reported by Schumacher and Miller*

Reported by	Date	Age and Sex	Treatment	Time After Injury Treated	Results	Comment
Sträuli, A.: Deutsche Ztschr. f. Chir. **136**: 167-226, 1916	1916	23 M	Expl. lap., packing of liver	1 hour	Died after 9 hours	Ruptured liver also present; ruptured duodenum not recognized; hematoma present
Korte 1904, cited by Melchior, E.: Neue deutsche Chir. **25**: 468-484, 1917	1917	22 M	Liver packed	22 hours	Died after 5 weeks	Duodenal rupture not found, duodenal fistula developed late
Söderlund, G.: Nord. med. Ark. **51**: 191-295, 1918	1918	42 M	1. Expl. lap. 2. Suture 2d day 3. Drainage psoas abscess 5th day	2½ hours	Died after 8 days	Hematoma first operation, bile staining 2d operation; not recognized at 1st operation
Harris, W. H.: Canad. Pract. **47**: 294-304, 1922	1922	Young M	Drainage only	4 days	Died same day	Retroperitoneal gas present
Harris, W. H.	1922	Young M	1. Suture 2. Jejunostomy at 12 days	About 20 hours	Died after 19 days	Retroperitoneal gas present; duodenal fistula at 10 days
Furtwaengler [6]	1922	24 F	Closure of duodenal fistula, gastroenterostomy	2 months	Died after 13 days	Pyopneumoretroperitoneum; spontaneous rupture in 5 weeks
Millet 1897, cited by Furtwaengler [6]	1922	22 M	Drainage only	8 days	Died after 2 days	Ascaris infection
Esau 1911, cited by Furtwaengler [6]	1922	13 F	Drainage of retroperitoneal abscess, nephrectomy	4 weeks	Died after 6 days	Kidney had been ruptured; duodenal fistula developed
Sandahl, O.: Acta chir. Scandinav. **59**: 55-67, 1925	1925	34 M	Suture	2½ hours	Well after 26 days	Retroperitoneal hematoma present
Naumann 1902, cited by Sandahl	1925	39 M	Drainage only	3 days	Died same day	Duodenal rupture not found
von Staplemohr 1916, cited by Sandahl	1925	32 M	Drainage only	Next day	Died shortly after operation	Duodenal rupture not found; fat necrosis present
Harrington, S. W.: S. Clin. North America **6**: 1185-1188, 1926	1926	19 M	Suture	Immediately	Died after 15 days	Duodenal fistula 6th day
Harrington	1926	11 M	Suture, splenectomy	1 hour	Died after 12 hours	Also had ruptures of intraperitoneal duodenum, liver and spleen
Rudofsky, F.: Beitr. z. klin. Chir. **40**: 314-319, 1927	1927	17 M	1. Suture 2. Jejunostomy 7 days	7½ hours	Well after 34 days	Emphysema present, duodenal fistula developed after 7 days
Krogius, A.: Finska läk.-sällsk. handl. **69**: 809-815, 1927	1927	21 M	Resection 15 cm. duodenum, duodenojejunostomy, enteroenterostomy	2 hours	Well after 41 days	Hemoperitoneum from retroperitoneal hematoma; evisceration 10th day
Róna, D.: Gyógyászat **67**: 1004-1006, 1927	1927	19 M	Appendectomy, suture	Next day	Died after 4 days	Retrocecal phlegmon involving appendix
Woodside, C. J. A.: Brit. M. J. **2**: 1225, 1927	1927	30 M	1. Suture, liver packed 2. Abscess drained 41st day	5 hours	Well after 79 days	Subphrenic abscess developed
Kantor, A.: Med. Klin. **25**: 264-265, 1929	1929	38 M	Suture, posterior gastroenterostomy	Immediate	Well	Bile staining present; duodenal fistula developed; incisional hernia repaired 2 years later
Davis [17]	1930	Young M	Suture, omental graft	2 hours	Well	Area of discoloration medial to kidney
Podlišič, I.: Zentralbl. f. Chir. **57**: 82-83, 1930	1930	14 M	1. Suture 2. Pseudocyst drained 11th day	6 hours	Well after 39 days	Bile staining and emphysema present; pancreatic pseudocyst developed
Leibowicz, M.: Zentralbl. f. Chir. **57**: 1278-1283, 1930	1930	26 M	Suture, anterior gastroenterostomy	16 hours	Died after 3 days	Bile staining present
Schmorell, H.: Zentralbl. f. Chir. **57**: 1919-1922, 1930	1930	Young M	Suture, anterior gastroenterostomy	6 hours	Well after 10 days	Bile staining present
Fischl, E.: Zentralbl. f. Chir. **58**: 18-19, 1931	1931	22 M	Suture, liver sutured	Immediately	Well after 3 weeks	Retroperitoneal hematoma, lacerated liver
Amberger, J.: Zentralbl. f. Chir. **58**: 14-15, 1931	1931	11 M	Suture	Soon	Well after 7 weeks	Anterior duodenal rupture also
Butler and Carlson [15]	1931	24 M	Suture, jejunostomy	9 hours	Died next day	Fat necrosis present, pain in both testicles unusual sign
Sudhoff [13]	1931	17 M	Suture	24 hours	Well after 2 months	Bile staining, fat necrosis present; bilateral parotitis, dehiscence of wound postoperatively
Brizio, G. V.: Policlinico (sez. prat.) **39**: 261-265, 1932	1932	Young M	Duodenal end closed, duodenojejunostomy; no drains	8½ hours	Died on 3d day	Retroperitoneal hematoma, superficial laceration of liver, complete duodenal tear, contusion of abdominal muscles
Seregby, E.: Zentralbl. f. Chir. **59**: 1165-1167, 1932	1932	21 M	Drainage	20 hours	Died shortly	Rupture not found at operation
Ciminata, A.: Policlinico (sez. prat.) **39**: 1326-1329, 1932	1932	16 M	Suture	4 hours	Well	Bile staining, slight emphysema of submesocolic area on right; communication with peritoneal cavity of exudate
Steinberg, G.: Arch. f. klin. Chir. **171**: 425-428, 1932	1932	24 M	Suture, gastroenterostomy	2 hours	Died after 8 days; pneumonia	Bile staining, intraperitoneal fibrin
Köhler [10]	1932	19 M	1. End-to-end anastomosis of duodenum 2. Anterior gastroenterostomy 10th day	14 hours	Well after 43 days	Complete tear; duodenal obstruction resulted on 10th day

TABLE 1.—*Cases of Retroperitoneal Rupture of the Duodenum in World Literature Up to May 1943 Exclusive of Those Reported by Schumacher and Miller—Continued*

Reported by	Date	Age and Sex	Treatment	Time After Injury Treated	Results	Comment
Laffitte, H.: Arch. franco-belges de chir. **34**: 117-125, 1934	1932	23 M	Suture	9 hours	Well	Bile staining present
Oberascher, H.: Zentralbl. f. Chir. **60**: 378-379, 1933	1933	66 M	Suture	1 hour	Well after 21 days	Local anesthesia, also had small prepyloric perforation
Mauro, M.: Ann. ital. di chir. **12**: 1402-1420, 1933	1933	48 M	Suture	8 hours	Died after 36 hours	Retroperitoneal bloody edema and fat necrosis
Blasker, M.: Brit. M. J. **1**: 283-284, 1934	1934	Young M	Sutured end-to-end	2 hours	Well	Retroperitoneal bile and hematoma; duodenum ⅔ ruptured; pancreatic fistula for short time
Krsek, H.: Bratisl. lekár. listy **14**: 390-394, 1934	1934	18 F	Exploratory laparotomy	7 hours	Died on table	Anterior and posterior rupture
Krsek, H.	1934	30 M	No operation	1 hour	Died after 1 hour	Head of pancreas mashed
Poindexter [11]	1935	51 M	Drained	18 days	Died same day	Large rent in duodenum, retroperitoneal cellulitis
Sperling and Rigler [10]	1937	19 M	No operation; continuous duodenal suction	20 hours	Well after 13 days	Roentgenogram showed much emphysema
Betto [9]	1938	15 M	Packed with iodoform gauze	2½ hours	Well after 18 days	Retroperitoneal hematoma, no perforation discovered at operation; duodenal fistula at 8 days when drain removed
Wyatt, O. S.: Minnesota Med. **21**: 792, 1938	1938	3 M	Suture	4½ hours	Well after 25 days	Retroperitoneal hematoma, also peritoneal leak of exudate
Lure, A. S.: Vestnik. khir. **53**: 771-772, 1938; Lurje, A.: Arch. Surg. **37**: 806-810, 1938	1938	30 M	Suture; also resection of ascending colon	6 hours	Died after 21 days	Retroperitoneal hematoma, emphysema laceration of colon; fistula of colon
Decoulx, P.: Rev. de chir., Paris **77**: 274-284, 1939	1939	49 M	Drainage	14 hours	Died after 2 hours	Total rupture of 3d portion; condition on table very bad; retroperitoneal emphysema, edema
Zaaijer, J. H.: Nederl. tijdschr. v. geneesk. **83**: 4101-4106, 1939	1939	22 M	Suture	6 hours	Well after 18 days	Edema under and above mesocolon
Holubec, K.: Zentralbl. f. Chir. **66**: 2586-2590, 1939	1939	21 M	Suture, packed liver	4 hours	Well after 29 days	Bile staining present, also lacerated liver
Hinton [12]	1940	13 M	1. Exploratory laparotomy, duodenal suction 2. Post. gastroenterostomy at 12 days	6 days	Well	Lesion not found at first operation
Ottenheimer, E. J., and Gilman, R. L.: New England J. Med. **222**: 251-253, 1940	1940	21 M	Exploratory laparotomy	3 hours	Died after 38 hours	Roentgenogram showed emphysema; ruptured duodenum not found at operation
Lomazov, M. G.: Novy khir. Arkhiv **48**: 239-241, 1941	1941	19 M	Drainage	8 hours	Died after 30 hours	Retroperitoneal emphysema, hematoma and bile staining; patient's condition bad before operation was completed
Braun, H.: Zentralbl. f. Chir. **68**: 1102-1109, 1941	1941	18 M	End-to-end anastomosis of duodenum, Billroth II gastric resection, enteroenterostomy	2 hours	Well after 4 weeks	Nearly complete duodenal tear; emphysema, bile staining present
Braun [13]	1941	50 M	1. Suture 2. Closure of colon fistula at 8 weeks	3 hours	Well after 3 months	Emphysema, blood and bile staining present; previous Billroth II, posterior, gastric resection, 3 years before; liver lacerated; pneumonia, wound disruption and fistula of transverse colon complications
O'Callaghan, D.: Brit. J. Surg. **30**: 107-112, 1942	1942	20 F	Suture, liver packed	8 hours	Well after 82 days	Also Colles fracture, lacerated liver; drainage from wound prolonged
Personal case	....	11 M	Suture	25½ hours	Well after 54 days	Bile staining, fat necrosis present

Köhler,[10] in 1932, reported a case which he states is the eleventh instance of cure of retroperitoneal rupture of the duodenum.

Poindexter,[11] in 1935, reviewed the literature for the period from 1925 to 1933, presenting 2 cases. He makes a sensible list of points to be considered.

Hinton,[12] in 1940, presented a summary of his review of the literature between 1910 and 1940 and gave the following statistics concerning traumatic rupture of the duodenum: 25 cases of anterior rupture, with 13 recoveries; 11 anterior and posterior ruptures, with 6 recoveries; 47 posterior ruptures, with 18 recoveries; 1 with location not stated, in which the patient recovered. This article is brief and the bibliography extremely incomplete.

10. Köhler, H.: Surgical Repair of Retroperitoneal Lacerations: Case, Deutsche Ztschr. f. Chir. **237**:756-760, 1932.

11. Poindexter, C. A.: Traumatic Rupture of the Duodenum, Texas State J. Med. **30**:561-566 (Jan.) 1935.

12. Hinton, D.: Rupture of the Duodenum by Blunt Trauma, J. Internat. Coll. Surg. **3**:485-490 (Dec.) 1940.

There are unusual cases associated with retroperitoneal injuries. I have not included Sudhoff's [12] second case in my table, as drainage of a retroperitoneal abscess occurred one year after the primary injury; no duodenal drainage resulted. Poindexter's [11] first case is somewhat similar. A retroperitoneal abscess drained seven days after injury, and no duodenal drainage resulted. Although there may possibly have been a small duodenal leak in this case, I prefer not to include this and Sudhoff's case in the table.

In Köhler's [10] second case there was bile staining of the retroperitoneal tissues and profuse drainage of bile from the retroperitoneal space for several weeks; but there was no visible rupture of the duodenum when this was mobilized, and apparently no duodenal fistula, but a biliary fistula, developed. This would seem to correspond much more to a rupture of the biliary tract as in a case [14] at the Union Memorial Hospital in which the common duct was ruptured by abdominal contusion.

Table 1 is meant to include all bona fide retroperitoneal ruptures of the duodenum which have been reported in the world literature up to May 1943 which were not reported by Schumacher [4] or Miller.[5] In the column labeled "treatment," when more than one operation was performed this is indicated by numbering each procedure; otherwise the entire list of procedures was performed at one time.

As can be seen by surveying the bibliography and table 1, there are few reports of cases of traumatic retroperitoneal rupture of the duodenum from this country. Cases reported indicate that with recognition of the condition and with proper treatment results can be good. Therefore I shall present in detail the points of diagnosis that can be utilized as derived from a study of the many complete reports of cases by many authors.

DIAGNOSIS

There is a history of a severe blow to the abdomen, not necessarily over the duodenum, that may not appear to be serious at first. In fact, the patient may be able to walk away from the scene of accident. Then, as extravasation progresses, there is an increasing spread of pain in the right side of the back, right loin and abdomen. Vomiting usually occurs when attempts are made to take anything by mouth, but nausea is not a prominent sign. Mild shock and signs suggestive of peritonitis are increasingly manifest, and operation is imperative. Pain in the testicles, as a diagnostic sign of retroperitoneal duodenal rupture has been reported,[15] but is rarely present. Increase in leukocytes up to 14,000 or more is common but not always present. The urine may contain red cells early from concomitant contusion of the kidney, and not infrequent is the finding of pus with clumping as the intestinal juices extravasate around the kidney and ureter. The roentgenogram may reveal emphysema about the right kidney; emphysema has been reported also as a finding on rectal examination in severe extravasation of gas.

At operation, there is frequently a small amount of "beef broth"-like fluid within the peritoneal cavity. Other intra-abdominal injuries having been ruled out or identified, the area lateral to the duodenum should be inspected. Occasionally fibrin may be found. Edema of the tissues is the most constant finding and increases as the time after injury increases. Staining of the tissues by bile when present is a most important diagnostic sign and ranges from a small green spot overlying a subperitoneal rupture to diffuse yellow staining together with hematoma or edema. Retroperitoneal hematoma is commonly seen. Emphysema is fairly common in this area, extending around the anterior fascial planes in severe cases. Fat necrosis is not often found, interestingly enough. Hemoperitoneum may of course be present when there is an associated lacerated liver, spleen or pancreas or when there is leaking from the retroperitoneal hematoma into the peritoneal cavity.

Of concomitant injuries, laceration of the liver is the most common. When this injury occurs one should not neglect considering the possibility of a retroperitoneal rupture of the duodenum. Rupture of the spleen, multiple ruptures of the bowel, contusion of the pancreas and occasional fracture have been reported with rupture of the duodenum; but it is interesting that this entity exists so often as the only serious injury present.

Table 2 presents some of the most important additional pathologic conditions in our series, to give a general idea of their relative occurrence. It is to be remembered that many reports are not complete, and that therefore this table does not represent the entire number of times these signs occurred.

The prime diagnostic difficulty is similar to that of any intestinal rupture due to blunt trauma to the abdomen, and that is to decide which patient may be safely watched, and which must be operated on immediately. Berry [16] has made this apt statement: "The great majority of such

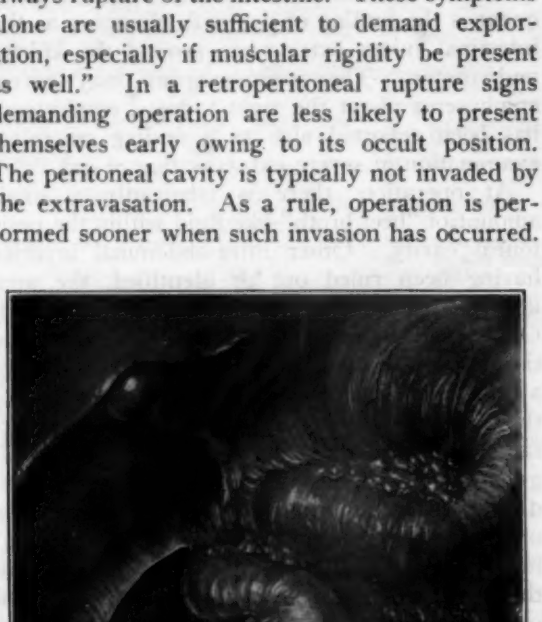
13. Sudhoff, W.: Wounds and Injuries of the Duodenum, Arch. f. klin. Chir. **164**:829-839, 1931.

14. Finney, J. M. T., Jr.: Personal communication to the author, February 1943.

15. Butler, E., and Carlson, E.: Pain in Testicles: Symptom of Retroperitoneal Traumatic Rupture of Duodenum, Am. J. Surg. **11**:118 (Jan.) 1931.

16. Berry, J.: Diagnosis and Treatment of Injuries of the Intestines, Brit. M. J. **2**:643 (Oct. 22) 1921.

cases (abdominal contusion) recover without operation. But a blow upon the abdomen, followed by severe and continuous localized pain and marked local tenderness, indicates almost always rupture of the intestine. These symptoms alone are usually sufficient to demand exploration, especially if muscular rigidity be present as well." In a retroperitoneal rupture signs demanding operation are less likely to present themselves early owing to its occult position. The peritoneal cavity is typically not invaded by the extravasation. As a rule, operation is performed sooner when such invasion has occurred.



Mobilization of duodenum by the division of the peritoneum and rolling the duodenum forward exposing hole.

TREATMENT

It is obvious that on reasonable suspicion of retroperitoneal rupture of the duodenum, operation should be performed immediately. In most of the cases in which cure is obtained the patients are operated on within the first ten hours after rupture although, as my own case illustrates, more than twenty-four hours may elapse with a successful conclusion.

A list of cases in which various procedures have been successful may be of aid, although in any case the surgeon must make an intelligent effort to overcome the existing lesion by reestablishing normal function.

At operation proper exposure is the most important single factor, both in determining the extent of the lesion and in its repair. For lesions down as far as the inferior flexure of the duodenum Kocher's maneuver of mobilizing the duodenum by lateral incision of the peritoneum, as shown in the accompanying illustration, is best as it can be rapidly done, allows excellent exposure of the retroperitoneal duodenum and is relatively safe. For lesions of the inferior flexure of the duodenum, lying in the submesocolic area, approach by retracting the colon cephalically and dividing the mesocolon will give excellent exposure and in fact is recommended by some authors as the procedure of choice. Here, however, the middle colic and superior mesenteric vessels lie close and the technical hazard is thus increased.

When the lesion has been identified, as a rule the less done the better the chance of the patient to recover. Simple suture obviously fulfils this criterion. In the case here reported, as in most of those described, the mucosal edges were clean, signifying a blowout effect, not a crushing lesion of the bowel; such a lesion is amenable to suture as the surgeon desires, remembering that there is no peritoneal surface and its sealing effect is not present. I think the omental graft as employed in a case by Davis [17] is an improvement,

TABLE 2.—*Simultaneously Occurring Pathologic Conditions in Series of Cases Under Consideration*

	No. of Cases
Retroperitoneal bile staining	16
Retroperitoneal hematoma	13
Retroperitoneal emphysema	13
Rupture of liver	9
Fat necrosis	5
Intraperitoneal rupture of bowel	4
Contusion of pancreas	1

TABLE 3.—*Successful Procedures Reported*

	Schumacher [4] 1910	Miller [5] 1910-1916	Present Report 1916-1943
Simple suture	1	1	16
Suture and omental graft	..	..	1
Suture and gastroenterostomy	..	1	2
End-to-end anastomosis	..	..	2
End-to-end anastomosis, Billroth II gastric resection, enteroenterostomy	..	..	1
Resection of injured duodenum with duodenojejunostomy	..	1	..
Resection of duodenum with duodenojejunostomy and enteroenterostomy	..	..	1
Resection of duodenum with duodenojejunostomy and gastroenterostomy	1	..	..
Continuous duodenal suction with late gastroenterostomy	..	..	1
Continuous duodenal suction	..	..	1
Packing of injured area	..	..	1
Total survivals	2	3	26
Total cases reviewed	23	29	52

17. Davis, C. B.: Injury to Abdomen wtih Explosion of Viscus, S. Clin. North America **10**:265-266 (April) 1930.

to be used if there is any doubt as to the efficacy of closure. Duodenal fistula is a common sequel.

There have been several instances of nearly complete or complete severance of the duodenum, which can occur subperitoneally, and end to end anastomosis has been successful. In one such case,[10] obstruction of the anastomosis occurred and a secondary gastroenterostomy was necessary. Regarding a complementary gastroenterostomy, which has been advised by some surgeons as proper in all cases, I believe that this is to be reserved for those cases in which the repair has impinged to an obstructive degree on the lumen of the bowel. Reliance should be placed on an indwelling stomach or duodenal tube to put the repaired bowel at rest in the usual case. Anterior and posterior gastroenterostomies have alike been utilized as complementary therapy.

Braun [18] suggested performing a gastric resection in lieu of gastroenterostomy as the incidence of jejunal ulcers will thereby be reduced. It is to be remembered here again that this is an added procedure; therefore it would not seem to be the procedure of choice.

When there has been a crushing injury it has been necessary on occasion to resect a portion of the duodenum. This usually obviates any duodenoduodenal anastomosis, for both ends are fixed. Closure of the distal end and anastomosis with a loop of jejunum have been found successful in such cases. One of the most complicated cases in which cure was obtained was that of Enderlen, cited by Schumacher,[4] in which it was necessary to resect the duodenum from just below the ampulla of Vater to the duodenojejunal flexure. The ends were closed, and a gastroenterostomy was performed. Then, with the patient in satisfactory condition, a duodenojejunostomy was performed to give an outlet for bile and pancreatic juices.

Theoretic considerations concerning possible rupture of the duodenum at the point of the ampulla of Vater have been presented by several authors, in which various procedures of exclusion with reanastomosis of the gallbladder, pancreatic and biliary ducts to the jejunum or stomach are advanced. Statistics do not show any ruptures at this point, however, which may be due to the physical strength that does not give way to internal or external forces.

Drainage is a most important part of the treatment, its importance increasing as the time between injury and operation increases. Because of the nature of the lesion, it is mainly in the retroperitoneal space that the cellulitis is located and it may extend to the opposite side and down into the pelvis. When the duodenum is mobilized a direct peritoneal opening to this area is provided. While the peritoneal cavity cannot be adequately drained, the area overlying the injury can and should be. The extraperitoneal space can be adequately and extensively drained by stab wounds in the posterior part of the flank and lower lateral area of the abdomen, the wounds necessary being of course in direct relation to the extent of infiltration present. Previous authors have not stressed extraperitoneal drainage, but the lateness of operating in the case presented, the extent of the infiltration and the subsequent late development of a retroperitoneal abscess all have made me more interested in this point. One counterincision cannot drain the retroperitoneal space on one side adequately.

Local application and systemic use of the sulfa drugs should be added to the treatment that I have described unless contraindications exist.

Sperling and Rigler [19] presented a case in 1937 in which the diagnosis was arrived at by indirect evidence. Roentgenograms showed emphysema of the retroperitoneal tissues and later, after ingestion of barium, a deformity of the second portion of the duodenum. The physical findings were concordant with a retroperitoneal duodenal rupture. The patient recovered after treatment with simple duodenal suction for ten days, but I believe the gods were smiling here. Extravasation has been prevented at least in 1 reported case (cited by Schumacher [4]) by actual blockage of the perforated area by blood clot. However, this fortunate circumstance is most unusual and in most instances there is a wide open lesion. Thus duodenal suction cannot be accepted as anything more than accessory treatment to proper surgical measures. The roentgenographic evidence of emphysema from a ruptured duodenum is of course a valuable aid in diagnosis, and its presence should mean immediate laparotomy.

It is to be noted that Hinton's [12] patient was treated by continuous duodenal suction for six days before the first operation, at which time the rupture was not found, and that a gastroenterostomy without closing the duodenal tear was performed six days later with successful result.

COMPLICATIONS

Too frequently the cause of death is not given in reports of cases; but, aside from general injuries, there appear to be two primary reasons for unsuccessful treatment—peritonitis and retroperitoneal cellulitis. Table 4 lists other compli-

18. Braun, H.: Rupture of the Duodenum by Blunt Trauma, Zentralbl. f. Chir. **68**:1102-1109 (June 14) 1941.

19. Sperling, L., and Rigler, L. G.: Traumatic Retroperitoneal Rupture of Duodenum: Description of Valuable Roentgen Observation in Its Recognition, Radiology **29**:521-524 (Nov.) 1937.

cations arising within the abdomen in the series of cases considered in this paper.

Pulmonary complications are not unusually frequent. Breakdown of wounds is more common than in routine abdominal operations and is a point against placing drains through the incision.

TABLE 4.—*Serious Intra-abdominal Complications (Excluding Cellulitis and Peritonitis)*

Condition	No. of Cases	Comment
Duodenal fistula	8	Three recoveries
Pancreatic fistula	1	Recovery
Subphrenic abscess	1	Recovery
Duodenal obstruction	1	Recovery; following end-to-end anastomosis
Pancreatic pseudocyst	1	Recovery
Fistula of colon	2	Right portion of colon resected in 1 case

SUMMARY AND CONCLUSIONS

Retroperitoneal rupture of the duodenum by blunt trauma to the abodmen is an unusual condition which is difficult to treat successfully. Diagnosis even during operation is often missed. The literature between 1916 and 1943 reveals 52 cases, in 26 of which cure was obtained. In 7 of these 52 cases the lesion was not found at operation.

One additional case of retroperitoneal rupture of the duodenum presented is the thirty-second case of successful treatment reported in the entire literature on the subject.

It is necessary to individualize the treatment in each case, but the basic factors, besides general preoperative and postoperative care, to be considered in curing a patient with retroperitoneal rupture of the duodenum are:

1. Correct diagnosis at operation. Whenever edema, staining by bile, hematoma or emphysema occurs over the retroperitoneal area of the duodenum, the surgeon must explore.

2. Closure of the rupture.

3. Short circuiting operation, only if the closure of the rupture produces obstruction.

4. Proper drainage of the peritoneal cavity and the retroperitoneal space.

5. Stomach or duodenal tube to put the traumatized area at rest.

6. Intelligent use of the sulfa drugs.

Many complications may arise following treatment of retroperitoneal rupture of the duodenum, the most serious of which are peritonitis, retroperitoneal cellulitis and duodenal fistula.

ORAL ADMINISTRATION OF DIETHYLSTILBESTROL FOR PROSTATISM

A CLINICAL EVALUATION

WILLIAM KLEIN, M.D., AND BERNARD NEWMAN, CH.E., M.S.
NEW YORK

A frequent and persistent complaint of the aged man is inability to rest at night due to frequent urination. In our institution, we have an opportunity to observe over 200 men whose ages range from 67 to 98 years. Many of these men are unwilling to undergo prostatectomy or are poor risks for such a procedure. Hence we have attempted to alleviate their condition by the oral administration of diethylstilbestrol.

Noble,[1] soon after the effects of diethylstilbestrol had been noted, reported that male rats after treatment with diethylstilbestrol exhibit atrophy of the testicle and decrease in the size of the seminal vesicles and the prostate. Mellish, Baer and Macias,[2] using an experimental group of 39 rats which had received implantations of 10 mg. of diethylstilbestrol twenty-eight days previous to autopsy, found the mean weight of the prostate to be 20 mg. In an untreated group of 23 controls, they observed the average prostate to weigh 102 mg.

Huggins and Clark [3] noted that after periodic injections of large doses of diethylstilbestrol into 7 senile dogs the prostate glands decreased in size.

One of the earliest reports on the treatment of benign prostatic hyperplasia in human beings is that of Kahle and Maltry.[4] These observers stated that treatment with testosterone not only has no effect on the hyperplastic prostate but at times seems actually to stimulate the gland to further hyperplasia. Hence the authors resorted to the use of diethylstilbestrol. They used as their experimental group 14 men between the ages of 51 and 80 years, who were treated with diethylstilbestrol parenterally. Their nocturnal frequency of urination and other concomitant symptoms were ameliorated, and in every patient a decrease in the size of the prostate was noted on rectal examination. The authors reached the conclusions that the administration of estrogenic substances produces definite changes in the glandular elements of the hyperplastic prostate; that moderately enlarged glands regress to normal size and even atrophy with complete relief of symptoms, while very large glands decrease in size and in an appreciable number of cases even return to normalcy, and that hyperplasia of the prostate can probably be controlled by adequate therapeutic and maintenance doses of diethylstilbestrol.

A review of the literature on the interaction between the prostate, the pituitary and the gonads and the treatment of prostatic hyperplasia with diethylstilbestrol dipropionate was reported by Colon.[5] He treated 9 patients with hypertrophy of the prostate by intramuscular administration of diethylstilbestrol dipropionate. All of his patients unquestionably benefited. The number of nocturnal urinations decreased, and the longer periods of rest had a marked beneficial effect on their well-being. Rectal examination of all his patients showed a definite decrease in the size of the prostate, and catheterization revealed a decrease in the amount of residual urine. While Colon also employed prostatic massages as a form of therapy, it is well known that this treatment alone could not account for the results he obtained.

A study was made by us of the effects of the oral administration of diethylstilbestrol on prostatism in old men.

EXPERIMENTAL PROCEDURE

Twenty-five men, ranging in age from 68 to 94 years, were examined. Their chief complaint at the time was frequency of nocturnal urination and other concomitant

From the Surgical Division of the Hospital and Home of the Daughters of Jacob.

1. Noble, R. L.: Effect of Synthetic Estrogenic Substances on Body Growth and Endocrine Organs of Rat, Lancet **2**:192, 1938.

2. Mellish, C. H.; Baer, A. J., and Macias, A. C.: Experiments on the Biological Properties of Stilbestrol and Stilbestryl Dipropionate, Endocrinology **26**:273, 1940.

3. Huggins, C., and Clark, P. J.: Quantitative Studies of Prostatic Secretions: Effect of Castration and of Estrogen Injection on Normal and on Hyperplastic Prostate Glands of Dogs, J. Exper. Med. **72**: 747, 1940.

4. Kahle, P. J., and Maltry, E.: Treatment of Hyperplasia of the Prostate with Diethylstilbestrol and Diethylstilbestrol Dipropionate, New Orleans M. & S. J. **93**:121, 1940.

5. Colon, J. E.: Tratamiento medico de la hiperplasia prostatica, Bol. Asoc. méd. de Puerto Rico **34**: 41, 1942.

disturbances, such as a sense of pressure and pseudopriapism.

A history of each patient's urinary complaints was taken. A rectal examination of the prostate was made, and the size, consistency, anatomic landmarks and other pertinent data were noted and recorded. The subjects were then catheterized after having voided in order to determine the amount of residual urine.

Specimens of blood were obtained after a fast of at least eight hours, and the following constituents were determined: urea nitrogen, acid phosphatase, sugar and total and esterified cholesterol. Twenty-four hour specimens of urine were collected and preserved with toluene, and the daily excretion of creatine and creatinine was determined.

Administration of small doses of diethylstilbestrol [6] was begun. This substance was administered orally in the form of enteric-coated tablets and was given twice daily, in the morning and in the evening. Patients in this age group are often uncooperative and imbued with some degree of superstition and hence cannot be entrusted with medicine to be taken in privacy. We therefore arranged for the administration of the diethylstilbestrol by the intern staff daily at specified hours.

Subjects were observed biweekly, and oftener when some unforeseen occurrence was reported to the staff. All prostatic examinations were performed by one of us (W. K.).

The table shows, in condensed form, the salient features of our observations.

Summary of Effects of Oral Administration of

Case	Age	Chief Complaint	Rectal Examination	Residual Urine, Cc.	Maximum Dosage: Mg. per Day	Maximum Dosage: Period of Medication	Effect of Medication
1. B. I.	67	Nocturnal urination, four times; sensation of pressure; occasional dribbling	Very large prostate; soft; anatomic markings normal	Not determined	0.75	9 weeks	Uninterrupted sleep from 11 p. m. to 6 a. m.; sensation of pressure and dribbling gone
2. A. S.	86	Nocturnal urination six to eight times; burning and pain on micturition	12/17/42: Large senile prostate; soft	120	1	12 weeks	Burning and pain disappeared; nocturnal urination reduced to one time
3. I. S.	77	Nocturnal urination five times	12/17/42: Small prostate; hard	Not determined	5	4 months	Nocturnal urination unimproved
4. N. K.	82	Nocturnal urination four times	12/31/42: Extremely large prostate; firm at the periphery	Not determined	2.5	12 weeks	Nocturnal urination reduced to two times
5. S. A.	80	Nocturnal urination five times; almost constant dribbling	12/17/42: Moderately enlarged prostate; firm	180	2.5	8 weeks	Nocturnal urination reduced to three times; dribbling somewhat less
6. S. M.	76	Nocturnal urination four times	12/17/42: Enormously enlarged prostate; soft	Not determined	3	12 weeks	Nocturnal urination reduced to one time
7. B. L.	64	Nocturnal urination eight to ten times; continual dribbling	3/2/43: Moderately enlarged prostate; very hard	Could not be obtained; patient had hypospadias	3	9 weeks	Nocturnal urination diminished; dribbling less
8. J. G.	85	Nocturnal urination four to five times	1/7/43: Moderately enlarged prostate; hard	15	3	13 weeks	Nocturnal urination reduced to two times
9. B. P.	71	Nocturnal urination four to five times	12/28/42: Very large and soft prostate; anatomic markings well defined	50	2	13 weeks	Nocturnal urination reduced to one time
10. N. H.	77	Nocturnal urination seven or eight times	12/17/42: Large and soft prostate	90	3	5 months	Nocturnal urination reduced to three times
11. A. R.	73	Nocturnal urination hourly; each voiding preceded by severe spasm	12/22/43: Large and soft prostate; some induration at lower end	Not determined	3	12 weeks	Nocturnal urination reduced to two times
12. A. B.	67	Nocturnal urination three or four times	12/18/42: Moderately enlarged prostate; very hard; anatomic landmarks not well defined	60	3	4 weeks	None
13. S. H.	77	Nocturnal urination five or six times	12/17/42: Very large prostate; soft	60	4	14 weeks	Nocturnal urination reduced to two times
14. B. S.	81	Nocturnal urination six times	2/2/43: Extremely large prostate; soft	50	3	10 weeks	Nocturnal urination reduced to two times
15. L. R.	80	Nocturnal urination two or three times; pseudopriapism	12/18/42: Moderately enlarged prostate; normal in consistency	Not determined	2	14 weeks	Uninterrupted sleep through the entire night; priapism subsided
16. D. A.	71	Nocturnal urination five times	1/21/43: Much enlarged prostate; firm	Not determined	3	16 weeks	Nocturnal urination reduced to two times (large stream)
17. L. H.	71	Nocturnal urination four times; sense of pressure	5/12/43: Tremendously enlarged prostate; soft	Not determined	3	5 weeks	Nocturnal urination reduced to two times; no sense of pressure

COMMENT

As mentioned previously, the beneficial effects of diethylstilbestrol on benign hypertrophy of the prostate have been reported by a number of observers. We were, however, unable to find reports of synthetic estrogens' having been administered orally for such a condition. There is an obvious advantage for all concerned if the desired effects can be obtained by giving diethylstilbestrol orally. We were fully aware of the differences between oral and parenteral administration of any drug, both in its effects and in its dosage. Since persons show a wide variation in their reaction to diethylstilbestrol, one must determine the dose for each subject, starting necessarily with small amounts. In our series

6 Bought on the open market from a reliable manufacturer.

of cases, the tolerance of the subjects varied so much that no attempt was made to determine a minimum effectual dose or a maximum dose that could be tolerated without unpleasant side reactions.

An interesting observation was one that bears out the report of Ravich,[7] who found that among Jewish patients with hypertrophied prostates the incidence of carcinoma was 1.7 per cent, as compared with 20 per cent among all other patients with a similar condition. His suggested explanation that circumcized men are less prone to carcinoma is interesting. In this institution, there are over 200 men, all of whom are circumcized and whose ages range from 65 to over 95 years. The incidence of prostatic carcinoma among these men is very low, being slightly over 1 per cent. In the group under consideration, no evidence pointing toward either local or metastatic carcinoma was noted during the period of observation. We are not unmindful of the possible carcinogenic properties of the synthetic as well as the natural estrogens. In the short period during which these subjects were under study, we were unable to observe any carcinomatous effects. The fact that our subjects are of an advanced age group and may die from intercurrent diseases before many years affords us but little opportunity to study this phase of the problem.

In evaluating the effect of any medication on persons in an advanced age group, one must take care in interpreting their verbal responses to any inquiry. We were therefore reluctant to treat those patients whose mentality was shrouded. Twenty-three of our group were ambulatory and not under treatment for any other disease. Two were hospitalized (one for chronic arthritis and the other for a nonpathologic fracture). It was observed early in our experiments that those men who were physiologically younger

Diethylstilbestrol on Prostatism in Old Men

Subsequent Rectal Examinations	Complications	Total Time of Observation	Comment
2/18/43: Prostate reduced in size, corresponds to average in a man of 40 years; firmer. 4/5/43: Prostate smaller than on previous examination and much firmer	Both breasts indurated and painful at end of nine weeks; medication discontinued; relief in two weeks	6 months	At present patient sleeps through night; feels young again
4/5/43: Prostate markedly decreased in size; much firmer	At end of three months painful and indurated breasts; medication discontinued; complete relief in two weeks	6 months	Patient remains free from all symptoms referring to urinary bladder
5/28/43: No change in size or consistency of prostate	None	5½ months	No beneficial effects noted
5/17/43: Prostate reduced to about one half the previous size	None	5 months	Patient in hospital division due to nonpathologic fracture of neck of femur
3/2/43: Prostate somewhat smaller than on previous examination	None	5 months	Patient improved little
3/30/43: Prostate smaller and firmer	Enlarged and painful breasts at end of twelve weeks' medication	6 months	Improvement continues; patient had a transurethral resection done four years previously
5/25/43: Little change in size and consistency of prostate	None	12 weeks	Beneficial effects questionable
4/19/43: No changes noted	Nausea, eructations and anorexia	13 weeks	Complications cleared up in a few days after medication was discontinued
4/5/43: Prostate reduced to about half previous size; somewhat firmer	Nausea, vomiting at end of three months' medication	5 months	Improvement continues; gastric symptoms disappeared within a few days after medication was discontinued
6/1/43: Prostate much reduced in size; somewhat firmer	None	6 months	Improvement is slight
4/19/43: Prostate decreased to about half previous size	None	5½ months	Patient refuses further cooperation because he feels well
5/19/43: Condition of prostate unchanged	None	5 months	Patient in hospital; bedridden due to chronic arthritis
4/23/43: Prostate much smaller and firmer; upper pole easily reached	Indurated painful breasts	6 months	Induration and sensitivity of nipples persisted for five weeks
5/17/43: Prostate reduced in size; firmer	Development of sublingual adenitis and stomatitis, which cleared up five days after medication withdrawn	4 months	That the adenitis was a complication of diethylstilbestrol therapy is questionable
5/31/43: Prostate somewhat smaller; much firmer	None	5½ months	Patient states loss of power for sexual intercourse
6/14/43: Prostate much smaller and firmer	None	6 months	Symptoms only slightly ameliorated
6/17/43: Prostate moderately reduced in size; all other findings same	None	5 weeks	More improvement to be expected in the future

7. Ravich, A.: The Relationship of Circumcision to Cancer of the Prostate, J. Urol. **48**:298, 1942.

than their chronologic age responded to smaller doses of diethylstilbestrol.

It is therefore evident that the dosage will be generally in direct proportion to the degree of senility.

Another observation was that the younger, better preserved subjects were more apt to show complications resulting from diethylstilbestrol therapy than the others. The most frequent complication was changes in the mammary gland. Approximately 16 per cent complained of painful and swollen nipples. Examination revealed that the tissues surrounding the nipples were indurated and tender, while the nipples themselves showed little change. The indurated areas were slightly warmer to the touch than the rest of the body. It was not possible to determine at what dose this complication occurred, but at the time our patients complained of this untoward effect their prostatic troubles were markedly improved. Medication was discontinued, and within one week the subjective symptoms subsided, but the induration persisted slightly longer.

Since the preparation of this paper, we have had the opportunity to examine 1 such enlarged breast.

N. G., aged 79, complained chiefly of nocturnal frequency of urination with occasional priapism. He had to urinate as much as eight times per night. Physical examination revealed a well nourished man, alert and not bedridden. The prostate by rectal examination appeared very large and rather soft. The anatomic landmarks were well outlined. Roentgen examination of the long bones failed to reveal any pathologic condition. He was given diethylstilbestrol in doses of 1 mg. daily for six weeks. At the end of this period he began to complain of painful nipples and enlarged breasts. Examination revealed that both breasts were enlarged to about the size of those of a girl 12 years old. The nipples were black and sensitive. The left breast was excised and sectioned.

Pathologic Report.—A section of the mammary tissue revealed as the most prominent feature cystic changes, which appeared to involve the ducts. These ducts were distinctly cystic and for the most part lined by a single layer of cuboidal epithelium with deeply staining nuclei and clear cytoplasm. In some of the ducts there was a tendency for the epithelium to be multilayered, but this was the exception rather than the rule. In 1 duct, however, there was a distinct multilayering of the lining epithelium, the superficial portion of which, bordering the lumen, appeared to have undergone metaplasia, the cells consisting of what appeared to be squamous cells. There was a moderate infolding of the lining of most of the ducts, and the intervening stroma showed some hyalinization and a moderate amount of interstitial edema. The skin overlying the mammary tissue showed no essential pathologic change.

Fig. 1 (× 30).—As compared with mammary tissue of a normal man in the same age group, there is an apparent increase in the number of mammary ducts.

Further Course.—Three weeks after the use of the drug was discontinued, the pain in the right breast disappeared and there was a notable reduction in its size.

Another side effect was a gastric disturbance. Only 2 of our 25 patients complained of nausea, eructations and anorexia. (We were aware of

the work of Chamelin and Funk,[8] whose experiments showed that liver extract reduced the toxicity of diethylstilbestrol, but we did not avail ourselves of this information.) The gastric symptoms were relieved within three days after the medication was withdrawn.

No other complications were noted.

As was pointed out previously, there were wide variations in the tolerance of the experimental subjects to diethylstilbestrol. Some subjects tolerated 5 mg. daily for as long as six weeks without ill effects, while others showed gastric or mammary complications within two weeks after taking 1 mg. per day.

writing 8 subjects whose last dose of diethylstilbestrol was given from three to five months ago. Their prostates have remained reduced in size, and the original improvement as to the frequency of urination and the other concomitant symptoms has persisted. One subject, whose chief complaint was pseudopriapism, was relieved at the end of one month's treatment with 1 mg. of diethylstilbestrol daily, and his symptoms have not recurred. Our observations are necessarily clinical, and we are cognizant of the limitations of clinical evaluation. However, our findings seem to corroborate the report of Kahle and Maltry.[4] On sectioning prostates of persons

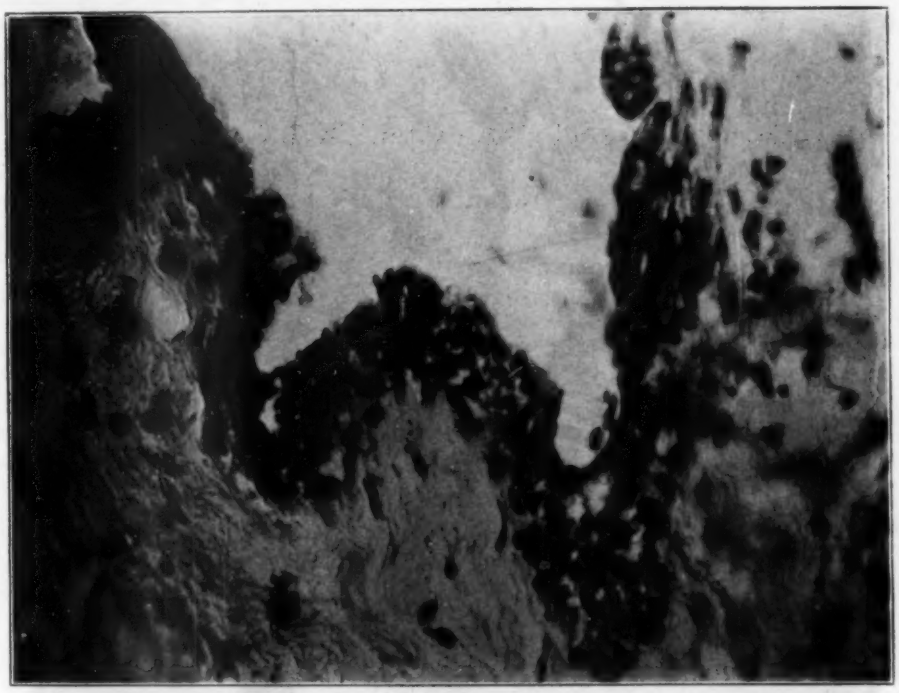


Fig. 2 (×60).—The ducts are hyperplastic, enlarged and dilated; the adjacent stroma is edematous.

Care must be taken that the greatest possible absorption occurs and that no other medication interferes with the maximum effect. Since many of these old men were in the habit of taking liquid petrolatum, which has been shown to interfere with complete absorption from the gastrointestinal tract, this form of medication was stopped. It is also known that diethylstilbestrol is soluble in oil and may pass through the body unabsorbed.

We had hoped that the effect of diethylstilbestrol on the prostate would be to reduce the size of the gland and that the resultant shrinkage would be lasting. We have at the time of

who had been under treatment with diethylstilbestrol they found:

1. A reduction in the number of papillary infoldings.
2. A decrease in the size of the acini.
3. A reduction in the height of the epithelium.
4. Stratification of the epithelium with and without vacuolization of the cells.

Further study of this problem is needed.

The following cases are typical instances of successes and failures of treatment.

Case 1.—B. I., aged 67, was well preserved for his age and able to carry on useful work in the institution. His chief complaint was nocturnal frequency of urination—four or five times. Occasionally there was a sense of pressure. Examination per rectum revealed a large, soft prostate with the central groove well outlined. The patient was given 0.5 mg. of diethylstilbestrol daily.

8. Chamelin, I., and Funk, C.: Action of Liver Extracts in Counteracting Toxic Effects of Diethylstilbestrol and Sulfanilamide, Arch. Biochem. **2**:9, 1943.

At the end of ten days the patient reported that the sensation of pressure had disappeared and that he now was getting up only once a night. The dose was increased to 0.75 mg. a day for one week and then to 1.25 mg. for a week. At the end of six weeks' treatment, the patient reported that he had been sleeping from 11 p. m. to 6 a. m. without interruption. Only on rare occasions he had a sensation of pressure during the day, but he complained of pain in both nipples. Examination revealed that both areolar areas around the nipples were indurated and tender. The prostate was reduced to about half the size but appeared somewhat harder in consistency. All medication was then discontinued. Within two weeks all subjective and objective signs of induration around the nipples had disappeared. The patient was reexamined three months after administration of diethylstilbestrol had been stopped. The prostate appeared even a little smaller than at the last examination, and none of the urinary complaints had recurred.

Fig. 3 (× 90).—The lining cells of the ducts are duplicated; their nuclei are hyperchromatic. A thin secretion is present within the lumen.

CASE 2.—A. S., aged 86, had had a suprapubic prostatectomy fifteen years previously. The improvement after that operation was only moderate. The patient still had to urinate twice nightly. The frequency of nocturnal urination increased as time progressed, until at the time of our first examination, on Dec. 17, 1942, urination occurred every two hours, accompanied by pain and a burning sensation. Examination at this time revealed a large prostate, soft in consistency with anatomic markings not well delineated. There was a moderate stricture at the anus, apparently caused by a hemorrhoidectomy some years previously. The patient was given 0.75 mg. of diethylstilbestrol daily. One month later he reported that there was definite improvement. The same dose was given for another month. The patient reported that the burning and the pain on urination had disappeared and the amount of urine voided each time was greatly increased. The dose was increased to 3 mg. daily for a month. At the end of this time, nocturnal urination was reduced to twice, but the subject complained of painful sensations in both breasts. Examination revealed the usual induration and sensitivity in the tissues around the nipples. Treatment with the drug was then discontinued. The patient was examined two months later. Findings at that time were as follows: The prostate was greatly reduced in size and firm in consistency; all mammary signs had disappeared; the patient still urinated twice nightly.

CASE 3.—I. S., aged 77, was examined on Dec. 17, 1942. His chief complaint at that time was nocturnal frequency of urination—five to six times—with no pain. Rectal examination revealed a rather small prostate, firm in consistency, with normal anatomic landmarks. It was rather surprising to find such a small, hard prostate. The patient was then given a general physical examination to rule out the possibility of cancer. No signs of either local or metastatic carcinoma were found. The blood acid phosphatase was within normal limits. The patient was given 0.5 mg. of diethylstilbestrol daily. After taking the drug for one month, he reported no improvement. The dose was then increased to 1.5 mg. daily for one month, after which time no improvement was reported. The dose was then increased to 3 mg. a day for a month, with but little subsiding of his symptoms. The amount was finally increased to 5 mg. daily for three weeks. This time there was a reduction in frequency of urination to three to four times nightly. Examination of the prostate at this time showed it to be somewhat smaller but with no distinct change in consistency.

This case illustrates the point that pronounced beneficial effects cannot be expected in the shrunken, hard prostate.

From a study of the accompanying table and the cases reported, it may be noted that considerable improvement may result from comparatively small doses of diethylstilbestrol in favorable cases, while in other cases large doses may fail to give the desired effect. It is therefore important to treat each patient individually and the doses should be regulated by close observation of his progress. As a general statement, we may say that in a person who is well preserved for his age and mentally alert and whose prostate is of the general hyperplastic type (senile hyperplasia) favorable results can be expected with this particular kind of estrogen, while in one who is suffering from advanced arteriosclerosis and its concomitant mental state or in one whose urinary obstruction is due to fibrous bars and sclerosis of the wall of the bladder good results cannot be expected.

As may be seen from the table, only 17 cases are tabulated. The other 8 cases have not been observed for a sufficient length of time to be included in a summary of results.

The criterion for success or failure was, of course, arbitrary. We were, however, reluctant to classify patients as improved unless the number of nocturnal urinations was reduced by at least 50 per cent. In the light of this criterion, there were 71 per cent who were improved or completely relieved. Of the remaining 29 per cent, only 1 subject showed no change in either the number of nocturnal urinations or the condition of the prostate. The other 6 patients showed varying degrees of improvement. It is therefore evident that the majority of men in our series were greatly benefited by this form of therapy. Two of the subjects complained of prostatism with an average frequency of nocturnal urination of five times. They had had suprapubic prostatectomies ten and three years ago respectively.

Complications occurred in approximately 25 per cent of the patients. Eighty per cent of these complications consisted of enlargement of the mammary glands, while the rest were gastric. None of these were severe enough to cause disability or to require confinement in the hospital. These complications occurred only when the maximum dose for the person was continued from three to four weeks.

SUMMARY

Twenty-five patients with prostatism were treated by oral administration of diethylstilbestrol. The majority showed distinct improvement.

Complications occurred in 25 per cent of the patients, all of which cleared up soon after medication was discontinued.

The resultant shrinkage of the prostate remained for at least six months. Whether this shrinkage is permanent will be shown by future examinations.

Dr. S. Seidenberg, senior resident physician, and Miss Annette Block gave their assistance.

PROSTHETIC RESTORATIONS FOR THE BREAST

TECHNIC USING SPONGE RUBBER

ADOLPH M. BROWN, M.D.
CHICAGO

A prosthesis (*πρόσθεσις*, a putting to, from *προστιθημι*, to put to) is an artificial substitute for any missing part of the body. Since most such corrections are for facial deformities and defects, much of the literature and the interest is concerned with facial restorations.[1]

In 1942 I[2] described a prosthesis for the restoration of the defect caused by the amputation of the breast and presented the technic of its construction. That paper was concerned with the restoration of the breast after surgical ablation. With modern education patients suffering from diseases of the breast seek earlier consultation; carcinomas of the breast are seen in and removed from younger persons. For want of something better, women who have undergone amputation of the breast attempt esthetic correction of the defect by wearing brassieres filled with various materials, e. g. cotton, lamb's wool, upholsterer's hair and goose down. The brassieres must be worn rather snugly to give a sense of firmness and security. Perspiration is therefore troublesome, and swimming, beach lounging and dancing become esthetically hazardous pastimes for these women.

Another class of patients who seek cosmetic correction are women with congenital atrophy or absence of the breasts. They attempt to give the outline of the breasts a semblance of acceptability by wearing brassieres filled with soft materials.

The problems of these two classes of patients are different. Patients with surgical amputation of the breast require:

1. Unilateral prosthetic correction (since generally only one breast is removed).

2. The restoration not only of the breast tissue but of the pectoralis muscle on the side of the operation.

3. A prosthetic breast is constructed and designed so that when the natural breast, which usually is not perfect and often is pendulous, is lifted to its normal position the natural and the artificial breast will match as to size, shape, site and position of the nipples.

Women with congenital absence or atrophy of the breasts require:

1. Bilateral restorations.

2. No replacement of lost muscle.

3. No correction of ptosis of the skin of the breasts. I make two types of breast prostheses:

1. Latex, hollow pneumatic prostheses molded in plaster of paris.

2. Sponge rubber, flexible elastic prostheses of commercial rubber molded under heat and pressure in aluminum molds.

TECHNIC FOR LATEX, HOLLOW PNEUMATIC PROSTHESES

The patient is placed in an upright position for measurements to determine the position of the artificial breast and the position of its nipple. As illustrated, a line is drawn along the length of the clavicle from the angle of Louis to the acromion process (AB). The measurements are made bilaterally. Another line (AD) is drawn vertically from the sternoclavicular notch to the xiphoid cartilage. With the arms dependent at the sides a line drawn from the acromion to the olecranon process is measured and bisected. On each arm a mark is placed 1 cm. below this point of bisection. A line (CC') is drawn from this mark on each arm across the chest. The clavicular lines (AB, AB') are bisected (E), and a line is drawn from the midclavicular line (E) of the normal side to the

1. Brown, A. M.: Correction of Facial Defects with Latex Prostheses, Arch. Otolaryng. **35**:720-731 (May) 1942; Extensive Mutilating Facial Defect: Cosmetic Correction with Latex Mask, Surgery **12**:957-961 (Dec.) 1942. Bulbulian, A. H.: An Improved Technique for Prosthetic Restoration of Facial Defects by Use of a Latex Compound, Proc. Staff Meet., Mayo Clin. **14**:433-439 (July 12) 1939. Lederer, F. L.: Prosthetic Aids in Reconstructive Surgery About the Head: Presentation of a New Method, Arch. Otolaryng. **8**:531-554 (Nov.) 1928. Peluse, S.: A Simplified Technic for the Construction of Life Masks of Latex Rubber, ibid. **31**:955-965 (June) 1940. Zinsser: Ein einfacher Nasenersatz, München. med. Wchnschr. **60**:2734 (Dec. 9) 1913.

2. Brown, A. M.: Latex Prosthesis for Cosmetic Restoration of the Amputated Breast, South. Surgeon **11**:181-188 (March) 1942.

nipple. Where this line crosses the line *CC'* is the ideal location for the nipple (*E'*). A measurement is made of the distance from the midsternum to the point established as the ideal site for the nipple on the normal side of the chest (*DE'*). The same distance is measured on the side of the operation, also along the line *CC'*, to determine the site for the artificial nipple. A small object, such as a bead or a button, is glued to the skin as a landmark. Now the patient is ready for the making of a negative impression. Petrolatum or liquid petrolatum is lightly applied to the side of the chest having the defect. The material for the negative impression may be ordinary molding plaster or one of the agar-molding compounds. Three pounds (1.3 Kg.) of ordinary no. 1 molding plaster is mixed with 1 pound (0.5 Kg.) of potato starch. This is mixed with water in a rubber mixing bowl and spread over half of the chest. The mold should extend laterally as far as the midaxillary line and should include the shoulder and the clavicle above. Thinner plaster furnishes finer detail. The patient is cautioned that the plaster will become warm as it hardens and is told to breathe lightly to limit costal excursion. Then the hardened plaster is removed and painted with a thin coat of petrolatum or dental separating compound.

A positive reproduction of the chest can be made of various plasters. Hydrocol, hard dental stone, hard molding plaster and rapid dental laboratory stone are all satisfactory. The plaster is made into a creamy paste by mixing it with water in a rubber bowl. Then it is spread thickly over the negative mold. The negative is gently tapped to remove bubbles and allowed to dry. The positive mold is removed from the negative impression by immersing both in hot water and separating them with a strong knife. The potato starch in the negative mass tends to swell in the hot water and forces the negative mold to disintegrate. The positive mold is gently cleansed and is ready for the sculpture of the new breast.

Prostheses are molded with various materials. Dental wax is used for some, but for a part as large as the breast modeling clay is more convenient and inexpensive. The model, however, must be kept damp during the entire process of modeling. Plasticine made with fine clay and olive oil is excellent and does not need to be kept damp.

When the plaster is poured for the positive impression, the embedded bead or button serves as a guide to locate the position of the new nipple of the sculptured model. A toothpick or an applicator inserted at this point serves as a marker. The modeled breast is made slightly larger in all dimensions, to allow for a small amount of shrinkage in the rubber. The borders of the modeled breast should be smoothed to feather edges.

Fig. 1.—*A*, amputation of breast for carcinoma. Note scar extending into axilla and loss of pectoral muscle mass. *B*, photograph showing ptosis of remaining breast.

In the modeling of a new breast, not only must the breast be duplicated but extra mass must be provided on its lateral aspect to compensate for the loss of the pectoral muscles which have been removed surgically. If the operative scar extends to the axilla, much of the scar and the consequent axillary distortion can be covered by an extension of the prosthesis.

Most women use brassieres to support the breast that has not been operated on. The restoration on the side of the operation is modeled not to the more or less pendulous outline of the remaining breast but with its contour idealized

and the nipple at its artistic site. Thus when the brassiere is worn, it serves to keep the restored breast in its position and to lift the other breast to its normal place.

Fig. 2.—Method of calculating the ideal position for the nipple with the remaining nipple used as a landmark.

Once the prosthesis is modeled satisfactorily as to size, position and artistic fidelity, it is ready to have the pores of the skin reproduced, as well as the details of the nipple. To reproduce the pores of the skin, a small amount of freshly mixed plaster is poured over the skin of the remaining breast and dabbed over an area 2 or 3 cm. in diameter. As it hardens, a wooden applicator is inserted to serve as a handle, and when the plaster is hard it is removed and used as a tamp or an impressor to stamp the pores and the delicate skin tracery into the clay model.

The nipple may be reproduced in the same way from the normal nipple. The erectile muscles are stimulated with cold water; fast-setting hard plaster is poured over the erect nipple and after hardening is removed. If the negative impression presents undercuts, they are gently shaved away. This negative impression is pressed on the roughly modeled nipple and reproduces the pores with astonishing fidelity. To complete the positive mold, key openings are made in two or three places near the edge of the impression to insure accurate fit of the positive mold later. It is lightly coated with petrolatum, the sculptured area being avoided. This positive plaster mold will later become the bottom portion of a two piece mold. The positive cast bearing the sculptured breast is then covered with hard plaster. The parts of the mold are carefully pried apart and the clay washed out.

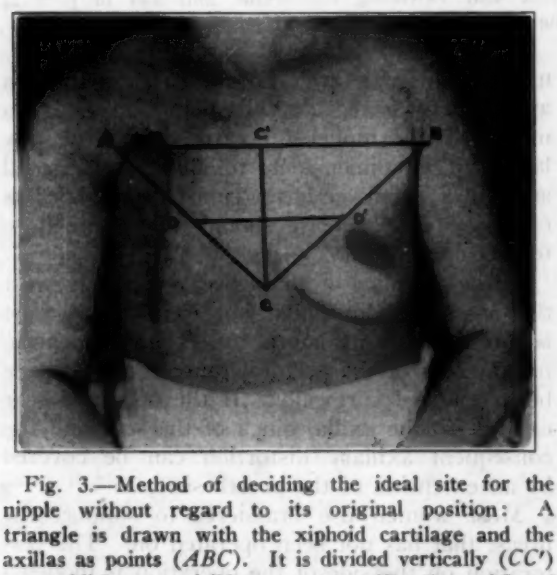


Fig. 3.—Method of deciding the ideal site for the nipple without regard to its original position: A triangle is drawn with the xiphoid cartilage and the axillas as points (ABC). It is divided vertically (CC') to establish more visible symmetry. The lines AC and BC are bisected, and the points D and D' furnish the sites for the nipples.

Fig. 4.—Latex prosthesis for unilateral restoration of the breast.

A passage for the poured rubber is then constructed. A conical opening is drilled through the bottom half of the mold, about 1 cm. in diameter at the narrow end and 4 or 5 cm. in diameter at the mouth. It is dug into the bottom part of the mold so that its approach is from the posterior, or hidden, side of the restoration. Now the mold is thoroughly dried, because the air content of the plaster is depended on to cure the rubber.

The type of rubber with which to cast is important. For this larger prosthesis a thick type of latex is used. Shrinkage is negligible,

and the product is firm. It may be thinned with a 28 per cent solution of ammonia.

Color is a vitally important factor in the achievement of a good prosthesis. Color added to the surface of a restoration only contributes to an artificial appearance. Color mixed with the latex before it is poured gives the restoration a nearly natural appearance with a translucence resembling that of normal skin. The colors used must be alkali-fast. Congo red, Biebrich scarlet and carmine red are suitable red dyes; burnt umber and iron oxide are satisfactory browns, and cadmium yellow and bismarck brown are also passable dyes.

Two paste colors which are stable in the presence of the ammoniacal diluent of the rubber are red CD paste and orange YOD paste.[3] They are made up of about 25 per cent active color and 75 per cent water and contain dispersing agents. The paste is diluted with a little ammoniated distilled water to obtain more delicate tints. If color agglomerates or specks appear on the finished latex prosthesis, one may assume that the colors did not disperse easily because they were not compatible with ammonia. This, we have found, is the most common reason for flocculation.

The mold is filled with rubber and is set aside for about forty-five minutes; then the excess rubber is poured out. A layer of rubber will remain coagulated against the plaster of paris jacket. It should be about ⅜ inch (10 mm.) thick. If it is not thick enough, the liquid latex may be poured into the mold a second time, adding to its thickness. When the layer is thick enough, the mold is placed in an oven at about 130 F. for approximately eight hours. If an oven is not available, it may be left at room temperature for one or two days.

After drying, the mold is opened and the restoration is inspected for bubbles, color and shrinkage. If the color is not right, an alteration of color is made, and a new pouring is necessary. Liquid latex is self vulcanizing; it coagulates on exposure to air. Thus plaster of paris permits the air to reach the rubber through the pores of the plaster. It also hastens coagulation by drawing the solution of ammonia off and into its own mass, the molded coagulum being left within the mold.

The edges of the prosthesis are trimmed with fine scissors and an electric burning pencil. The latter is a stylus with interchangeable points of various shapes. Seam lines may be obliterated with the heated knife edge, and irritating points on the skin side of the prosthesis may be trimmed away with it. The prosthesis may be ground smooth here and there with a high speed granite wheel, such as is used to trim vulcanite.

The prosthesis is hollow, and a few pinches of lycopodium are sprinkled or blown into the interior to prevent adhesions within the cavity. The openings through which the rubber was poured are sealed with a thin sheet of latex. Thus the prosthesis is pneumatically sealed. The imprisoned air together with the natural elasticity of the latex rubber compound gives resiliency to the restored breast, comfort to the wearer and esthetic satisfaction.

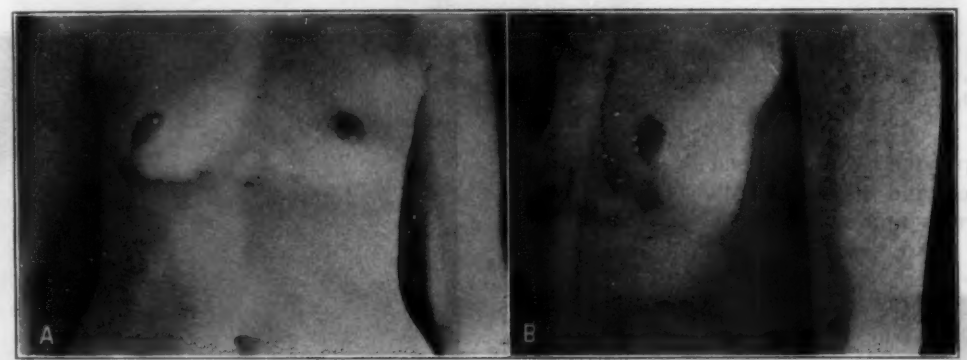


Fig. 5.—*A* and *B*, front and oblique views showing congenital atrophy of the breasts.

The prosthetic breast restoration may be held in place with a brassiere. For such activities as swimming or when a brassiere cannot be worn, it may be attached with a mucilage made of styrax, gum mastic and chloroform, which has been found nonirritating and convenient to use. Not only does it hold the prosthesis firmly in place, but it is perspiration proof and waterproof.

TECHNIC FOR FLEXIBLE, ELASTIC SPONGE RUBBER PROSTHESES

The patient is placed in an upright position, and measurements are made to determine the position of the artificial breasts and the position

3. E. I. DuPont de Nemours Company, Wilmington, ton, Del.

of the nipples as described with the preceding technic. The positive reproduction of the chest in hard plaster is also carried out in the same way. However, the entire chest must be reproduced. The new breasts are sculptured in clay slightly oversize to allow for shrinkage of the rubber. Since both breasts are being restored, much more freedom in the execution of the sculpture is permitted; no existing breast need be copied.

Fig. 6.—Coloration of the prostheses by application of tinted liquid latex. The plaster hood is applied immediately after the rubber is painted on, to insure a dull finish.

The prosthetist is governed by the stature of the patient and his own artistic sense. After the sculpture is finished, the mold is completed by pouring more hydrocol over the ensemble of

Fig. 7.—Patient putting prosthesis into position.

plaster chest and sculptured breasts. After it is hardened, the mold is taken apart and the clay washed out. This process leaves a two piece mold in plaster. Unlike the first technic, no pouring channel is made; instead the mold is cut along what would be the sternum, a die and a counter die of plaster of paris for each breast being left.

The plaster parts are now sent to the aluminum foundry for duplication in aluminum. Standard aluminum casting technic is used. A tiny opening, about 1/32 inch (10.8 mm.) in diameter, is drilled through the aluminum negative at the point of the nipple to permit the escape of air and carbon dioxide gas during the vulcanization of the rubber. It is necessary to use aluminum molds because sponge rubber prostheses are cured with heat under pressure.

The formula used for the sponge rubber prostheses is as follows:

Pale crepe rubber	18.0 lb. (8.2 Kg.)
Lead-free zinc oxide	1.0 lb. (0.5 Kg.)
Captax [4]	0.1875 lb. (85.1 Gm.)
Stearic acid	0.75 lb. (340.2 Gm.)
Petrolatum	6.0 lb. (2.7 Kg.)
Sodium bicarbonate	2.0 lb. (0.9 Kg.)
Sulfur	0.75 lb. (340.2 Gm.)
Glacial acetic acid	0.3125 lb. (141.8 Gm.)
15 per cent titanium dioxide (Diluted with Lithofoam [3])	2.5 lb. (1.1 Kg.)
T. X. red [3]	5 Gm.

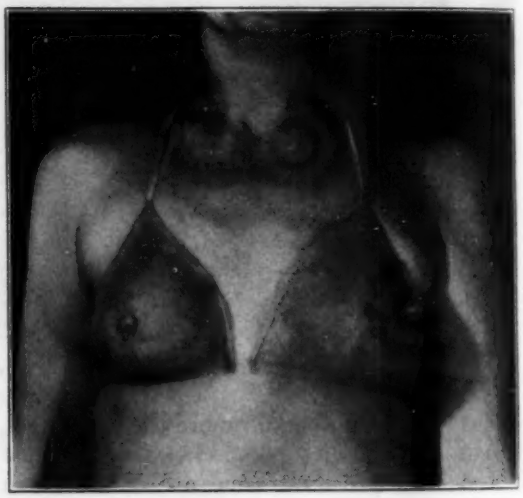


Fig. 8.—Front view with prostheses.

The amounts of the titanium dioxide and the T. X. red pigment are varied to furnish different shades of a basic color for the prostheses.

The various ingredients are incorporated into the mass with a milling machine. The milling machine consists essentially of two steel rollers eccentrically geared to run in the same direction at different rates of speed. The rubber mass is rolled repeatedly through the milling rollers to spread the components of the mass evenly through the batch of the pale crepe rubber.

After repeated milling, the rubber mass assumes the form of sheet rubber. A piece is cut with knife or scissors to fit the base of each mold. The mold is closed and locked under pressure

4. R. T. Vanderbilt Company, New York.

and then heated to 300 F. for approximately one hour. This heat liberates carbon dioxide in the form of countless numbers of tiny bubbles of gas, which expand the rubber and force it into every crevice of the mold. The excess gas escapes a few more times. This rolling pressure breaks the tiny partitions between the gas bubbles and gives the prosthesis a true sponge rubber consistency. Despite the distortion caused by the rolling, the prosthesis reassumes its vulcanized

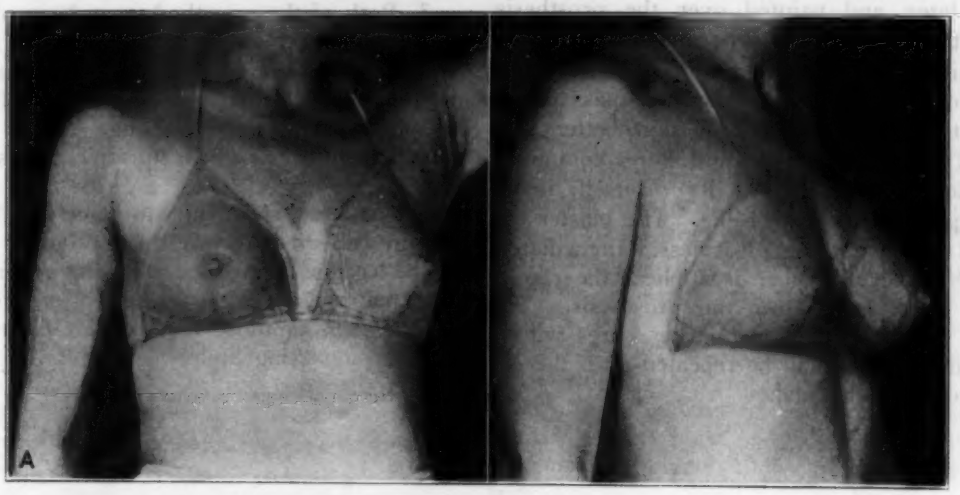


Fig. 9.—*A* and *B*, two oblique views with prostheses.

Fig. 10.—Side view with prostheses.

through the minute opening previously mentioned. Thus the rubber is forced into shape at the same time that it is expanded by the carbon dioxide gas, and it is vulcanized in the expanded state.

After the rubber breasts are removed from the mold, they are run through the milling machine shape. Breaking the trabeculae between the bubbles makes the prosthesis softer and more resilient. Most of the gas bubbles become true spongy air bubbles.

We have found that color applied to the surface of a prosthesis gives an appearance of artificiality to the restoration. To match the breast

prosthesis with the skin, the rubber breast is glued back on its aluminum base, and a cap of plaster of paris is poured over it. After drying, this cap is removed.

Suitable colors are mixed with a quantity of liquid latex and painted over the prosthesis. When the colors are incorporated with the rubber which is to become a part of the prosthesis, the color coming from within the mass of the restoration simulates that of skin better than painted colors. If the liquid latex containing the color is permitted to dry of itself, it becomes glossy and enamel-like. The plaster cap is used to prevent this glossiness. Immediately after the colored rubber is applied, the cap of plaster is replaced over the prosthesis. The rubber drying against the plaster cures with a dull finish. This may be repeated until the desired color is obtained.

The breasts may be fastened in place by the following methods:

1. They may be glued in place with a gum mastic mixture.

2. They may be held in place with a brassiere.

3. Both of these methods may be used simultaneously.

Sponge rubber prostheses wear exceedingly well. Although their production is involved and difficult, prostheses of sponge rubber should have a definite place in restorative reconstructive surgery.

We are now attempting to make prostheses of sponge rubber to restore the contour of the calf of the leg for the atrophy following poliomyelitis. This material should be useful too for large prostheses, such as those required for esthetic correction of missing limbs.

540 North Michigan Avenue.

INTRAVENOUS ADMINISTRATION OF FAT FOR NUTRITIONAL PURPOSES

EXPERIMENTAL STUDY

LUCIA J. DUNHAM, M.D.,* AND ALEXANDER BRUNSCHWIG, M.D.
CHICAGO

HISTORY AND PURPOSE

As early as 1895 Leube [1] raised the question of subcutaneous injections of fat for nutritional purposes, in connection with administration of repeated injections of camphor oil to patients with cardiac failure. Attempts were made by a number of workers [2] to study utilization of subcutaneously injected fat, although absorption from the sites of the injections was admittedly relatively slow. Studies on the utilization of emulsions of fats administered by vein to animals were made by Murlin and Riche in 1915,[3] Nomura in 1929,[4a] Baba in 1931 [5] and Narat in 1937.[6a, b] It was reported that by such injections the lives of 2 starving dogs were prolonged [6a, b] and in rabbits the iodine and saponification numbers of body fats were altered in the direction of those of the infused fats.[4b] While it was suggested that the infused fat was deposited in the depots, adequate control studies were not reported. Under certain circumstances the respiratory quotient was lowered by intravenous administration of fat.[5] Workers have used dyed or iodized emulsions intravenously [7] in attempts to trace the fate of infused fat, but conclusive evidence for utilization of such fat has not been obtained.

Mansfeld in 1918 [8] reported success in intravenous administration of fat emulsions to patients as a vehicle for quinine or camphor. Other workers who have reported on the intravenous administration of fat emulsions to human beings (adults, children and infants) are Valledor (1933),[9] Holt and co-workers (1935),[10] Gordon and Levine (1935),[11] Myers and Blumberg (1936),[12] Narat (1938),[6c,d] Frazer and Walsh (1939),[13] Krainick (1940) [14] and Clark and Brunschwig (1942).[15] The amounts of emulsion given daily to adults have varied from 20 cc.[13] to 250 cc.[8] and the lipid concentration has ranged between 3 per cent [8] and 10 per cent.[15] Beneficial effects were reported,[16] and depression of the respiratory quotient in a healthy infant was cited by Gordon and Levine [11] as suggestive evidence of utilization. Fat emulsions have been used to produce ketosis in the treatment of urosepsis [6c] and to "detoxicate" bacterial toxins.[10]

Recently casein digests have been successfully administered by vein to experimental animals and to patients, in addition to the dextrose and elec-

* Fellow, Swift and Company grant.

From the Department of Surgery, University of Chicago.

This work was carried out under a grant from Swift and Company, Chicago.

1. Leube, W.: Sitzungsb. d. phys.-med. Gesellsch. zu Würzburg, 1895, p. 5.

2. Koehne, M., and Mendel, L. B.: J. Nutrition **1**:399, 1929. du Mesnil [de Rochemont], T. F.: Deutsches Arch. f. klin. Med. **60**:472, 1898. Mills, L. H.: The Utilization of Fats and Oils Given Subcutaneously, Arch. Int. Med. **7**:694 (May) 1911. Mills, L. H., and Murlin, J. R.: Proc. Soc. Exper. Biol. & Med. **7**:166, 1909-1910. Sommer, G.: Sitzungsb. d. phys. med. Gesellsch. zu Würzburg, 1897, p. 26. Winternitz, H.: Ztschr. f. klin. Med. **50**:80, 1903.

3. Murlin, J. R., and Riche, J. A.: Proc. Soc. Exper. Biol. & Med. **13**:7, 1915.

4. Nomura, T.: (*a*) Tohoku J. Exper. Med. **12**:389, 1929; (*b*) **12**:497, 1929.

5. Baba, T.: (*a*) Tohoku J. Exper. Med. **17**:154, 1931; (*b*) **17**:274, 1931.

6. Narat, J. K.: (*a*) Arch. f. klin. Chir. **187**:795, 1937; (*b*) Am. J. Digest. Dis. & Nutrition **4**:107, 1937; (*c*) Urol. & Cutan. Rev. **42**:17, 1938; (*d*) J. Urol. **39**:75, 1938.

7. von Bodó, R., and Scheffer, L.: Arch. f. exper. Path. u. Pharmakol. **124**:326, 1927. Kimura, S.: Tohoku J. Exper. Med. **30**:315, 1937. Sato, G.: Tohoku J. Exper. Med. **18**:120, 1931. Saxl, P., and Donath, F.: Wien. Arch. f. inn. Med. **13**:7, 1926.

8. Mansfeld, G.: Wien. klin. Wchnschr. **31**:775, 1918.

9. Valledor, T.: Arch. de méd. d. enf. **36**:276, 1933.

10. Holt, L. E., Jr.; Tidwell, H. C., and Scott, T. F. M.: J. Pediat. **6**:151, 1935.

11. Gordon, H. H., and Levine, S. Z.: Respiratory Metabolism in Infancy and in Childhood: Effect of Intravenous Infusions of Fat on Energy Exchange of Infants, Am. J. Dis. Child. **50**:894 (Oct.) 1935.

12. Myers, R. J., and Blumberg, H.: Proc. Soc. Exper. Biol. & Med. **35**:79, 1936.

13. Frazer, A. C., and Walsh, V. G.: J. Pharmacol. & Exper. Therap. **67**:476, 1939.

14. Krainick, H. G.: Therap. d. Gegenw. **81**:60, 1940.

15. Clark, D. E., and Brunschwig, A.: Proc. Soc. Exper. Biol. & Med. **49**:329, 1942.

16. Holt, Tidwell and Scott.[10] Krainick.[14] Narat.[6d] Valledor.[9]

trolytes which have been used in routine clinical practice for many years. It seemed desirable to make further studies on the fate and possible nutritional properties of intravenously administered fat emulsions, because of the relatively high caloric value of fat and the possible indispensability of certain fatty acids for normal metabolism. Success in this direction would appear to afford further advance in the problem of supportive treatment of patients by parenteral feeding.

Studies on the lipids extracted from samples of omentum taken from dogs before and after intravenous infusions of fat were undertaken in an attempt to identify foreign fat in the normal fat depots of the body. Foreign fat that has been fed by mouth changes the normal body fat of animals.[17] If infused fat were found in the normal depots, it would presumably be destined to be utilized. Parallel with studies on the lipids, histologic observations were made on the liver, spleen and omentum before and after the infusions. The caloric intake, weight trends and blood and urine of the same animals were studied.

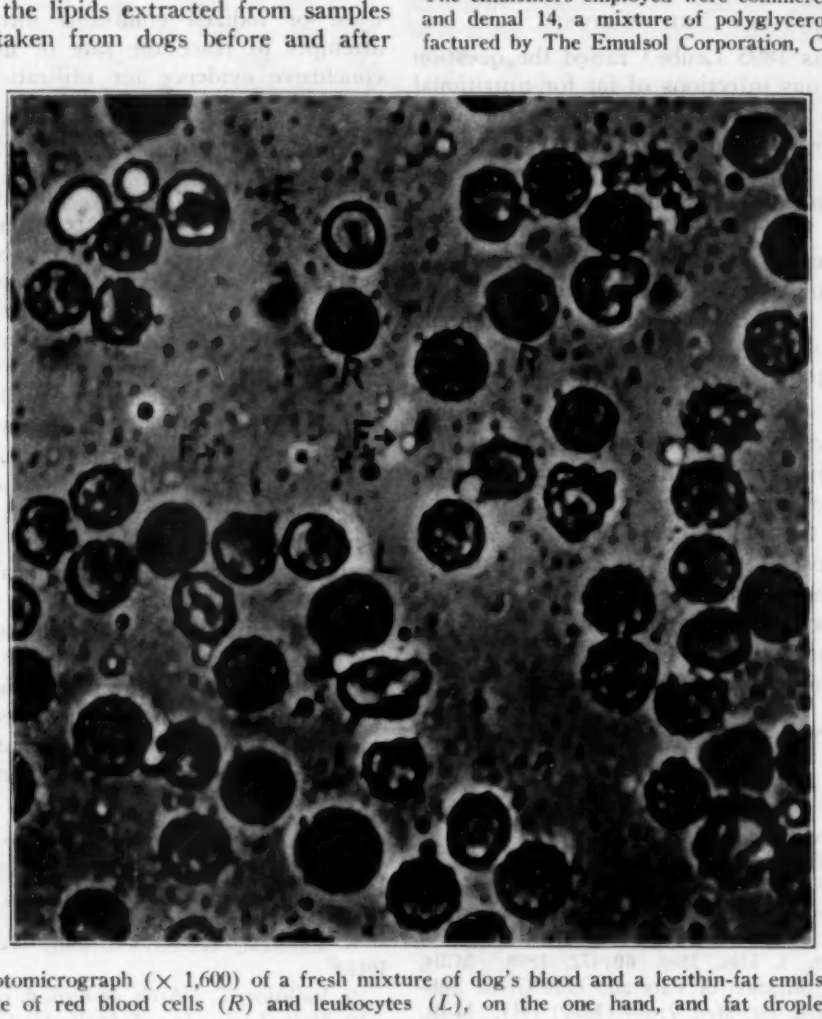


Fig. 1.—Photomicrograph (× 1,600) of a fresh mixture of dog's blood and a lecithin-fat emulsion to show the comparative size of red blood cells (*R*) and leukocytes (*L*), on the one hand, and fat droplets (*F*), on the other hand.

MATERIALS AND METHODS

Fat for intravenous injection was emulsified under high pressure. The emulsions were prepared by the combination of an emulsifier and a fat, in the proportion of one part of the former to two of the latter. The emulsifiers employed were commercial egg lecithin and demal 14, a mixture of polyglycerol esters manufactured by The Emulsol Corporation, Chicago (United States patent 2,022,766). The fats employed consisted of olive oil and lard oil (lowest melting point fraction of lard). A fat and an emulsifier were first stirred together in a large beaker. Gentle heating aided thorough mixture. A sufficient volume of distilled water was added to yield an emulsion that contained 4 to 7.5 per cent of the emulsifier and 10 to 15 per cent of the fat, by weight. Homogenization (emulsification) was obtained by passing the mixture through a dairy homogenizer at 4,500 pounds (2,025 Kg.) of pressure per square inch (the homogenizer was supplied by the Cherry-Burrell Corporation, Chicago).

At first tablets of sodium chloride were added to the emulsions to afford isotonicity, but these favored break-

17. Anderson, W. E., and Mendel, L. B.: J. Biol. Chem. **76**:729, 1928. Lebedeff, A.: Centralbl. f. d. med. Wissensch. **20**:129, 1882. Mendel, L. B., and Anderson, W. E.: Yale J. Biol. & Med. **3**:107, 1930. Munk, I.: Virchows Arch. f. path. Anat. **95**:407, 1884.

down of the emulsions. It was then observed that 5 per cent dextrose solution was a satisfactory menstruum. Autoclaving, carried out for sterility, also resulted in some creaming of the emulsions and was not generally employed when injections into animals were made.

Microscopic examination of samples of these emulsions in a hemocytometer chamber showed that most fat droplets varied in size from a fraction of a micron to 2 microns in diameter (fig. 1). Occasional droplets were as large as leukocytes, and some were 15 to 30 microns in diameter. The p_H of an emulsion of 7.5 per cent demal with 15 per cent lard oil in 5 per cent dextrose solution was 7.85; of the same type of emulsion with olive oil, 7.80, and with lecithin, 4.25.

Other emulsifiers were employed, such as soybean lecithin, "vegetable" lecithin and an anionic commercial emulsifier, which was hemolytic. All proved highly toxic.

The procedure for 13 dogs (table 1 *A*) was: (*a*) preliminary feeding for nine to fourteen days of commercial dog food of low fat content, 4 to 6 per cent, equivalent to 80 calories per kilogram of weight (but this was not always consumed); (*b*) biopsies of liver, spleen, omentum and occasionally kidney; (*c*) resumption of the preceding diet for four days with intravenous injections of isotonic solution of sodium chloride or infusions of 5 per cent dextrose solution in daily amounts equivalent to the volume of the fat emulsion that was injected daily after the fourth day. When the menstruum of the fat emulsion was saline solution, saline solution alone was injected in the preliminary period. The periods of infusions of fat lasted from one to thirty-six days. The quantities of emulsion infused daily were equivalent to 2 to 3 Gm. of fat per kilogram of body weight. Biopsies of liver, spleen, omentum and sometimes kidney were made at the end of the period of the infusions, and from 5 dogs specimens of liver, spleen, kidney, lung and omentum were taken at necropsy (animals killed) two to eight months after the last infusion. All animals that died during the experiment were subjected to necropsy. All tissues were fixed in a 4 per cent solution of formaldehyde and stained with hematoxylin and eosin or with sudan IV in frozen sections to detect fat. As controls, 3 dogs were maintained on the diet outlined and were subjected to biopsy at proper intervals but received no fat emulsions.

EFFECT OF INFUSED FAT ON QUALITY OF DEPOT FAT (TABLE 1 *B*)

Lipids were extracted from samples of omentum taken before and after the infusions, their iodine and saponification numbers determined and their physical states and melting points studied. It will be noted (table 1 *B*) that after the infusions the iodine numbers rose and the saponification numbers fell in all 9 cases. The iodine numbers of lard oil (2 samples) and olive oil were definitely higher than those of the omental fat of dogs taken at control periods, and the saponification numbers were definitely lower. The same was true of the emulsifying agent demal, also a lipid. Therefore, the changes tabulated might at first be interpreted as proving deposition of infused foreign fat in normal fat depots. However, in spite of preliminary feedings of the commercial dog food for ten days, 3 control dogs fed on this diet twenty-eight more days without infusions of fat showed similar shifts in the chemistry of their omental fat. In 2 dogs, A and S, fat was removed from the omentum four and a half and two and a half months after cessation of the infusions, feeding during these months having consisted of the stock laboratory diet. The quality of fat after this period resembled more closely the quality of fat before the infusions than that at the close of the twenty-one day periods of infusions and feedings of commercial dog food. We were led to conclude that changes in iodine and saponification numbers of depot fat were not appreciably affected by infusions of fat. The changes that were noted could be accounted for by the nature of the diet.

However, the physical states of the extracted fats of 4 of 9 dogs (E-1, A, 399 and 281) before and after the infusions did suggest changes in quality due to the infusions in these animals. The first samples obtained were predominantly solid at room temperatures. After the infusions the extracted samples at room temperature divided themselves clearly into fluid and solid fractions. In 1 instance the actual melting point of the fluid fraction was determined and found to be 11 to 12 C., identical with that of the infused lard oil. The physical states of the fats extracted from the control animals at the end of the experimental period were identical with those at the onset of this period; in 2 cases they were always solid and in 1 case always liquid (without solid fraction). Changes in color were noted in fats from both the control animals and those given infusions. The fats became more yellow or more orange, presumably as a result of the pigments derived from the diet of commercial dog food. Determinations of the melting point, which afforded a wide range of readings with the heterogeneous types of fat studied, were in general inconclusive. However, the melting points of the fats from dogs E-1 and A appeared definitely lower after the infusions than before, i. e. more like those of the infused fats. These physical changes presented suggestive but not conclusive evidence of changes in the quality of depot fat due to the infusions of fat in some of the animals.

HISTOLOGIC STUDIES

Biopsies before the infusions showed normal liver, spleen and omentum, and omentum examined after the infusions showed no abnormalities. Tissues taken after the infusions from 13 dogs in the studies described under "Materials and Methods" are here described with others taken after infusions of fat from 11 dogs in the studies on nitrogen balance (succeeding section). Altogether, of 14 dogs receiving lecithin emul-

TABLE 1.—*Effect of Infusions of Fat Emulsions on Depot Fat*

A. Infusion of Fat Emulsions into 13 Dogs							B. Lipids Extracted from Omentums Before and After Infusions of Fat *							
					Average Calories per Day per Kg.		Iodine Number		Saponification Number		Melting Points, C.		Physical States (Room Temperature)	
Dog	Emulsion	Days Infused	Status at End of Infusions	Weight Trend	In Food	In Emulsion	Before	After	Before	After	Before	After	Before	After
B	Egg lecithin 7% Lard oil 14%	8	Febrile, abscess of leg; killed	Stable	74	19	109	118	201	167	23-34	18?-43	Semisolid, pale yellow	Semisolid, pale yellow, orange flecks
E-1	Egg lecithin 7% Lard oil 14%	36	Good	Gain	78	25	100	121	211	196	35-40	16-43 (11-12)	White, granular and yellow fluid	White, granular and yellow fluid, mainly fluid
E-2	Egg lecithin 7% Lard oil 14%	17	Fair	Stable	49	25								
A	Egg lecithin 7% Lard oil 14%	21	Fair	Loss	34	24	79	106	234	191	36-42	14?-40	Solid, granular, white	Solid, granular and yellow fluid
T	Egg lecithin 7% Lard oil 14%	1	Died about 20 hours later	.....										
M	Egg lecithin 7% Lard oil 14%	13	Fair	Loss	18	24	83	97	205	203	22-45	20-45	Semisolid, pale white	Semisolid, pale white
275	Demal 4% Lard oil 14%	12	Died 12-20 hours later	Stable	55	19	98	105	198	191	28-44	28-44	Solid and fluid, yellow	Solid and fluid, orange yellow
E-3	Demal 7.5% Lard oil 15%	8	Poor, infusion stopped	Stable	69	22	119	...	189	...	18-44	.....	Solid and fluid, yellow	
661	Demal 7.5% Lard oil 15%	7	Died 6-20 hours later	Loss	49	22								
399	Demal 5% Lard oil 10%	8	Died 6-20 hours later	Gain	80	16	97	105	200	186	.....	.....	Mainly solid, pale yellow	Solid and fluid, pale yellow
8	Demal 4% Olive oil 14%	21	Good	Stable	41	13	101	118	194	189	20-45	20-45	Solid, pale yellow	Solid, orange yellow
281	Demal 7.5% Olive oil 15%	8	Died 4-5 hours later	Gain	64	18	105	117	199	186	20-44	20-44	Solid, pale yellow	Fluid and solid, yellow
409	Demal 5% Olive oil 10%	32	Good	Gain	69	17	88	105	197	192	18-35	18-35	Semisolid, pale yellow	Semisolid, yellow

				Three Control Dogs Average Calories per Day per Kg. in Food	Iodine Number		Saponification Number		Melting Points	Physical States	
		Days Fed	Weight Trend		Before	After	Before	After	Before and After	Before	After
283	Commercial dog food diet only	28	..... Slight loss	65	69	97	221	203	Identical	Solid, white	Solid, pale yellow
284	Commercial dog food diet only	28	..... Slight loss	80	94	101	212	201	Identical	Solid, white	Solid, yellow
286	Commercial dog food diet only	28	..... Slight loss	79	98	109	214	204	Identical	Fluid, white flocculum	Pale yellow fluid, white flocculum

* Qualities of fat infused: Lard oil: iodine numbers, 144 and 132; saponification numbers, 185 and 188. Olive oil: iodine number, 164; saponification number, 130.

sions, 5 died, 4 presumably as the result of the infusion, while the other (T) apparently had a severe renal lesion before the infusions were started. Of 10 dogs given infusions of demal emulsions (1 had previously been given infusions of lecithin emulsions), 5 died.

In dogs dying as a result of the infusions, globules of lipid in the tissues were larger in the dogs given demal emulsions and may well have exerted a serious mechanical interference with normal processes. Alveolar capillaries in the lungs were crowded and distorted with lipid globules, usually large, while the lungs of dogs given lecithin emulsions showed a smaller amount of fat in smaller globules, some of these engulfed by macrophages. In both groups increased but variable amounts of fat were seen in liver cells, in Kupffer cells and in the bile duct epithelium. In the dogs given demal emulsions, however, the hepatic sinuses were more heavily loaded with large fat globules, which compressed the liver cells (fig. 4). Fat globules in the spleen were larger in the dogs given demal emulsions and less frequently engulfed by macrophages (figs. 2 and 3). Lesions in the kidneys varied from small amounts of fat in the cells lining the convoluted tubules to larger amounts intertubularly and intratubularly and in the glomeruli. Dense casts were present in the renal tubules of 3 dogs that died during infusions of lecithin emulsions. Two control dogs (391 and 405) given infusions of a 10 per cent demal emulsion passed through the homogenizer in 5 per cent dextrose solution did poorly and showed unusually large globules of lipid in the tissues, perhaps because this preparation was coarser than true emulsions made up with oil.

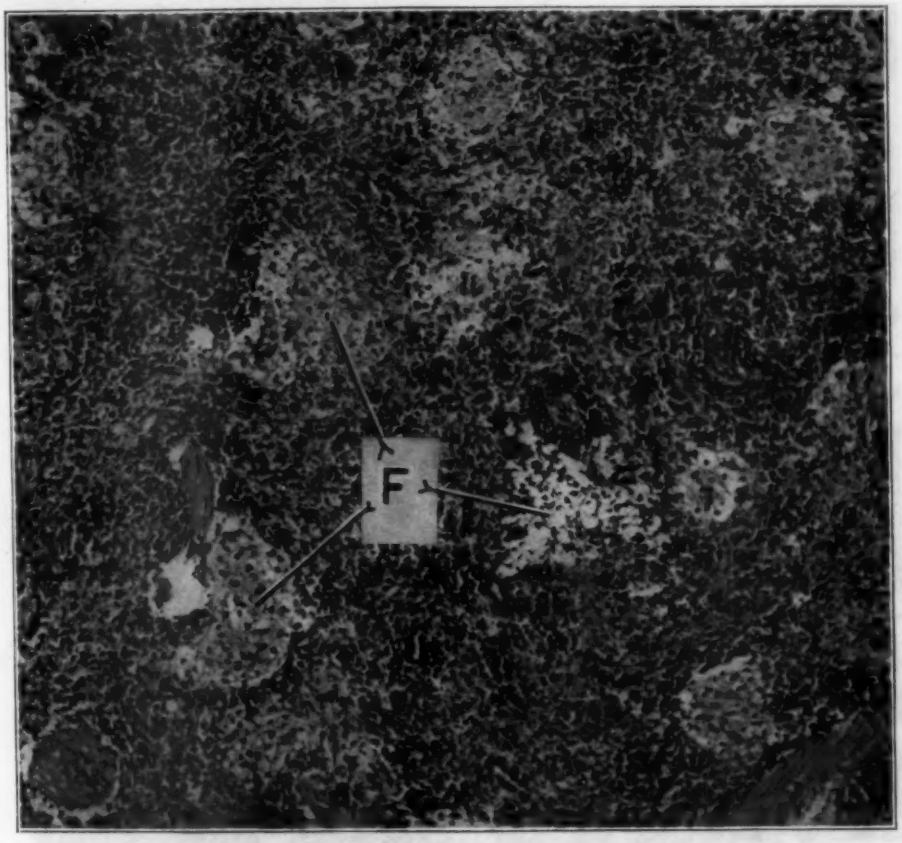


Fig. 2.—Photomicrograph of a biopsy section (hematoxylin and eosin stain) taken from the spleen of dog E-1 after thirty-six days of infusions of lecithin-fat emulsions. *F* shows foci of fat-filled macrophages (foam cells). Note absence of large vacuoles in the splenic sinuses due to large globules of fat, as when demal emulsions were infused (see fig. 3).

Liver and spleen of surviving dogs examined immediately after the period of infusions were similar to those described previously, except that liver of dog E-1 after thirty-six days of infusions was essentially normal in appearance. No outstanding differences were noted between the tissues of the surviving dogs given demal emulsions and of those given lecithin emulsions four weeks to eight months after the infusions. This is in contrast to differences in the size of the fat globules in dogs dying as a result of

256	Commercial dog food diet only	28	.....	Slight loss	79	98	109	214	204	Identical	Fluid, white flocculum	Pale yellow fluid, white flocculum

* Qualities of fat infused: Lard oil: iodine numbers, 144 and 132; saponification numbers, 195 and 188. Olive oil: iodine number, 104; saponification number, 190.

the infusions. Individual variations in disposal or in digestion of fat appeared to be not wholly related to the emulsifying agent or to the time that had elapsed since the infusions. The lungs of dogs given demal emulsions and of animals given lecithin emulsions were alike in being normal. The picture in the sections of liver varied from an essentially normal one to one showing the presence in the parenchyma of small groups of macrophages containing fat and brown pigment giving a prussian blue reaction identical with that of hemosiderin (fig. 5). Eventually both fat and hemosiderin appeared to decrease in amount and then disappear, leaving a few foreign body giant cells, not lipoid histiocytes (dog 499, three and a half months). In the spleen, as amounts of fat decreased, amounts of hemosiderin increased. Sections of kidney, which were for the most part normal or showed moderate amounts of fat in the glomeruli and tubules, showed in 1 case (dog 544) diffuse inflammation and fibrosis.

Mention has been made before of increased fat in the liver cells after infusions. The question arose as to whether this was injected fat or represented globules arising from within the cells as a result of injury incident to the infusions. It was not possible to stain fat in liver cells resulting from chloroform anesthesia by injection of sudan IV in diacetin (glyceryl diacetate) intravenously. The small amount of fat occasionally observed in normal liver cells was likewise not stained by such injections. In order to observe whether injected fat accumulated in the hepatic cells, the fat was saturated with sudan IV and the emulsion made and injected. The large globules of fat in the hepatic sinuses were stained light pink, but studies of the fat within the hepatic cells were inconclusive as to its staining; hence it was not possible to ascertain if the hepatic cell fat was exogenous or endogenous. Ten dogs were employed in this series of experiments.

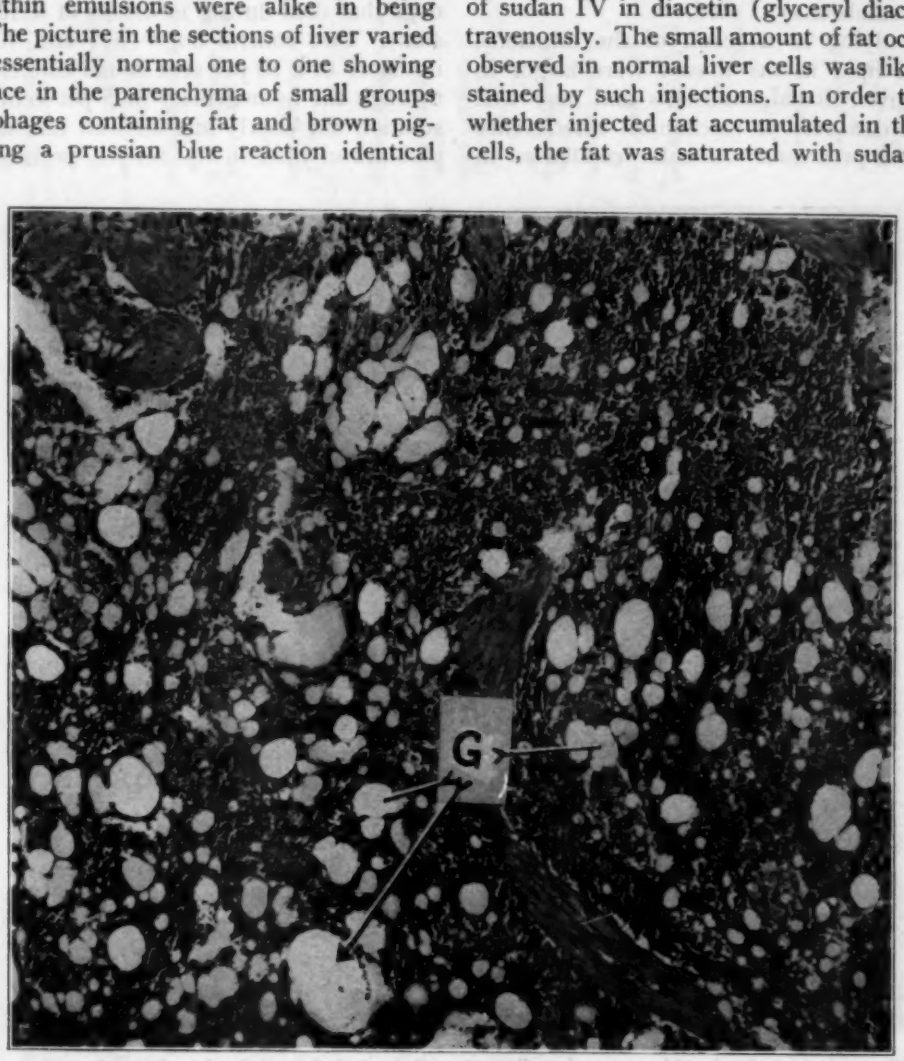


Fig. 3.—Photomicrograph of a biopsy section (hematoxylin and eosin stain) taken from the spleen of dog 409 after thirty-two days of infusions of demal-fat emulsions. Large fat globules (*G*) are not within the macrophages but are arrested in the sinuses.

THE RELATIONSHIP OF CALORIC INTAKE TO CHANGES IN WEIGHT

Of 12 dogs receiving infusions of fat and food by mouth, 4 gained weight, taking an average of

73 calories per kilogram by mouth and receiving an average of 19 calories of fat per kilogram by vein. Their gains in weight were equivalent to 3.4 to 10 per cent of the initial body weight over periods of eight to thirty-six days. Five dogs maintained a stationary weight but received an average of 57.5 calories per kilogram by mouth and 20 calories of fat per kilogram by vein. Three dogs lost weight, receiving an average of 34 calories per kilogram by mouth and 23 calories of fat per kilogram by vein. The gain or loss varied with the intake by mouth, the amount of fat infused having remained constant. Three control dogs maintaining caloric intakes of 65, 79 and 80 in food taken by mouth lost weight slightly. It is not possible to obtain evidence from these studies as to the extent of metabolism of the infused fat.

It will be noted that dog E (designated variously as E-1, E-2 and E-3) was given infusions of fat for three periods, a total of sixty-one days. It received a total of 1,724 Gm. of oil, exclusive of the lipids lecithin and demal, and biopsy specimens were taken four times. It showed a marked gain in weight (E-1) with infusions of fat when the total caloric intake was 103 calories per kilogram of weight. Weight was constant in the second course (E-2), in which a lecithin emulsion was given, and in the third course (E-3), with a demal emulsion, in which the dog showed malaise and weakness. Nine months later the animal appeared to be in vigorous health, had gained more than 3 Kg. in weight on the stock diet and was not anemic. Biopsy specimens of liver and spleen showed only small amounts of fat. Given infusions a fourth time, in the studies on nitrogen balance (designated as dog 250 in table 2), the dog survived the infusions for only four days. There was moderate portal cirrhosis of the liver, possibly the result of repeated prolonged injury to the liver by the infusions of fat. During the second course of infusions given this dog we observed on the second day an exophthalmos of the left eye, with dilated pupil and nictitating membrane covering about one third of the eyeball. This began to subside after five days and had disappeared eleven days later. This is the

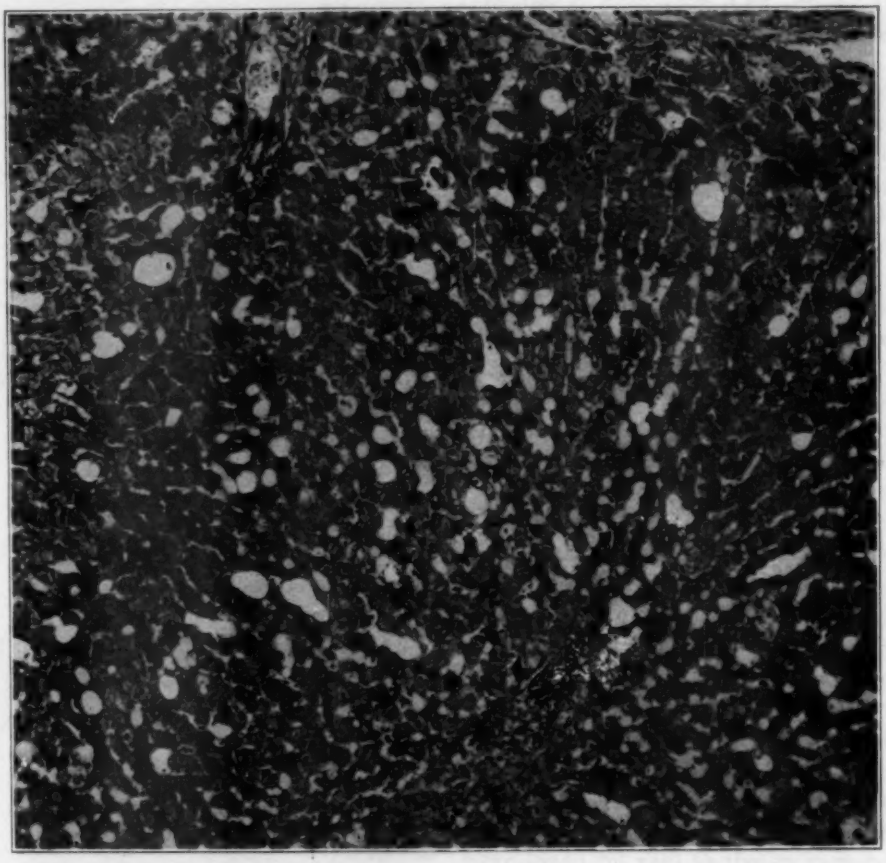


Fig. 4.—Photomicrograph of a biopsy section (hematoxylin and eosin stain) taken from the liver of dog 409 after thirty-two days of infusions of demal-fat emulsions. Large fat globules appear to distend and distort the hepatic sinuses.

only disturbance we observed that might have been the result of cerebral fat embolism.

BLOOD AND URINE OF DOGS GIVEN INFUSIONS

During the infusions of fat emulsions, the red blood cell count and the hematocrit reading were lowered for all dogs studied. Color indexes after the infusions did not vary significantly from those before the infusions. For 5 dogs with complete records the hematocrit readings fell to 55 to 73 per cent of the original values. The hematocrit readings of 3 control dogs fed the diet of commercial dog food for comparable periods fell to 83 to 91 per cent of the original values. Improvement occurred after cessation of the infusions, hematocrit readings returning to 86 to 94 per cent of the original values during periods ranging from two and a half to six months. The infusions of fat appeared to produce severe anemia in dogs, with recovery after the infusions were stopped and the dogs were returned to the stock diet. This is similar to what has been observed in the effects on the blood of high fat diets.[18]

In most instances the blood serum was clear twenty to twenty-four hours after the infusions of fat; in some instances it was cloudy. The white blood cell count rose conspicuously, to 19,800, 26,600 and 32,600 in 3 of 6 dogs on which observations were complete. Nomura [18] had observed in rabbits an early leukopenic response with subsequent leukocytosis.

No gross fat was seen in specimens of urine collected from dogs A and E over six day periods during the infusions of fat. However, ethyl ether extracts of 50 cc. aliquots evaporated to dryness showed a greasy film, which was proved to be fat by staining with sudan IV. We were led to conclude that a small portion of the infused fat was excreted in the urine, as might be expected from a histologic study of the kidneys, which in some cases showed the epithelium of the convoluted tubules loaded with small fat globules.

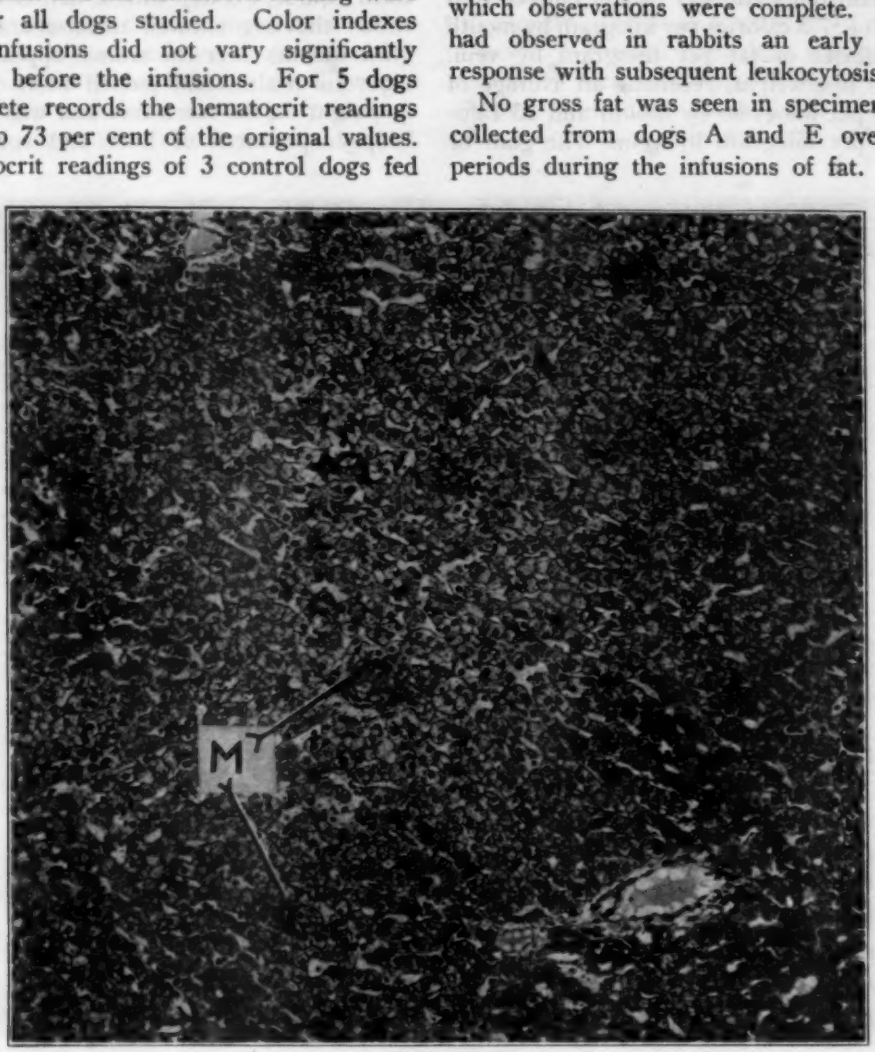


Fig. 5.—Photomicrograph of a biopsy section (hematoxylin and eosin stain) taken from the liver of dog 409 six months after the section shown in figure 4 was taken. Large globules of fat seen in the previous figures have now disappeared. *M* shows small foci of macrophages, some with hemosiderin and fat globules, scattered throughout the liver.

18. Johnson, V.; Longini, J., and Freeman, L. W.: Science **97**:400, 1943.

STUDIES OF NITROGEN BALANCE (TABLE 2)

Analysis of the depot fat in dogs given infusions of fat emulsions and histologic examination of their tissues had given no final proof of utilization of infused fat. Because of the nitrogen-sparing effect of fat on protein catabolism up to a point, studies were carried out to see if a reduction in excretion of nitrogen could be demonstrated as a result of the infusions of fat. Of 11 dogs used, 6 died, apparently as a result of the infusions. The others remained in good condition throughout the experiment.

The dogs were prepared by a preliminary starvation period of one week. Then 60 calories per kilogram of weight was given of the commercial dog food with a constant nitrogen content, and the urinary excretion of nitrogen was determined. Changes in weight were followed daily but did not prove to be significant. Each dog ate his daily ration, except those becoming ill for a day or two before death. For ten days the dogs were fed only by mouth; during the next ten days a 5 per cent solution of dextrose, 20 cc. per kilogram, was also given intravenously, and during a further period, of similar length, the same amounts of a 10 per cent olive oil emulsion in 5 per cent dextrose solution, instead of the dextrose solution alone, were given by vein. It was during this period that 6 dogs died, from three to nine days after the infusions were started. Five of the dogs during a fourth ten day period were again given only dextrose solution by vein, and 4 of these during a fifth ten day period were fed a fat emulsion by stomach tube in amounts equal to those previously given by vein.

TABLE 2.—*Excretion of Urinary Nitrogen of Dogs During Period of Infusion of Fat and Control Periods* *

Dogs	Commercial Dog Food Diet Only	Diet Plus 5% Dextrose Solution by Vein	Diet Plus Emulsion of Fat in 5% Dextrose Solution by Vein	Diet Plus 5% Dextrose Solution by Vein	Diet Plus Emulsion of Fat in 5% Dextrose Solution by Mouth
545	4.24	3.50	6.51 inc.	(Died 3 days after infusions were started)	
250	9.74	8.58	9.96 inc.	(Died 4 days after infusions were started)	
551	4.16	3.08	3.46 inc.	(Died 4 days after infusions were started)	
543	4.52	4.01	5.02 inc.	(Died 5 days after infusions were started)	
473	5.43	3.79	3.57 inc.	(Died 6 days after infusions were started)	
474	13.01	8.78	9.33 inc.	(Died 9 days after infusions were started)	
475	9.98	8.64	8.81	8.38	(In good health)
499	4.86	4.03	4.76	4.94	3.96
500	6.29	7.46	6.98	6.32	6.29
544	1.78	3.36	4.92	5.22	3.86
556	6.42	4.64	6.65	5.26	5.21

* All the figures represent averages (grams of nitrogen) of values determined for forty-eight hour periods. The period of each regimen was ten days.

There were frequent and wide variations among the five forty-eight hour determinations of nitrogen excretion within each ten day period. When these readings were averaged it was evident that the first period of administration of dextrose lowered the nitrogen excretion of 9 of 11 dogs and that when fat in addition was given by vein the nitrogen excretion fell still further in but 1 of the 5 dogs that survived and 1 of the 6 dogs that died during this period. There was not close agreement between the quantities of nitrogen lost during the periods of infusions of dextrose before and after the period of infusions of fat. A significant period in this study appeared to be the last, in which the levels of nitrogen excretion for 4 dogs fed a fat emulsion by mouth stayed relatively stable and all averages were below the corresponding ones obtained in the period of infusions of fat. It would appear that under the conditions of the experiment fat emulsions exert more of a nitrogen-sparing effect when given by mouth than when given by vein. Hence, when fat is administered by the intravenous route as outlined there appears to be little significant and profitable utilization of it. It thus seems likely, from the lack of nitrogen-sparing effect of infused fat in the dogs and the high mortality in this experiment, that the infusions of fat exerted a deleterious effect on the dogs.

Some confirmation of the absence of nitrogen-sparing effect following infusions of fat was found in studies on a patient. R. G., a man, aged 40, weighing 53.2 Kg., suffered from carcinomatosis. Nothing was taken by mouth during a nineteen day observation period when for eight days a casein digest (anigen) and dextrose were given by vein to the average equivalent of 1,052 calories per day. With this regimen the average nitrogen balance was + 1.7 Gm. a day. Then for eleven days a casein digest and dextrose were given to average only 852 calories per day. During this period an average of 21.6 Gm. of fat (olive oil) was also infused daily. The total caloric value of the substances given by infusion equaled 1,047, which was practically identical with the calories given daily during the first period of eight days in the form of a casein digest and dextrose only. It may be argued that if the infused fat were appreciably utilized, the caloric intake during the second period being the same as during the first, nitrogen balance should be

like that of the first period. However, during the second period there was a daily average loss of 0.8 Gm. of nitrogen, which suggests that the infused fat was not appreciably utilized. It is true that the intake of protein was less in the period of infusions of fat than during the previous period, when it averaged 1.6 Gm. per kilogram daily. During the period of infusions of fat it averaged 1.25 Gm. per kilogram daily, which is still appreciably above the commonly accepted minimum, of 0.75 Gm. per kilogram daily. A change from positive nitrogen balance to negative nitrogen balance of the degree cited previously would certainly not be anticipated if fat were appreciably utilized. Studies reported previously [15] on the intravenous administration of a casein digest, carbohydrate and fat to another patient showed maintenance of the patient's weight and of a positive nitrogen balance. While this patient did tolerate the infusions of fat well, it would seem in the light of these later studies that utilization of the fat did not occur. The case was reported as an example of the apparent innocuousness of intravenous injections of fat. A necropsy performed a year later on the patient afforded no evidence of permanent severe damage as a result of the infusions of fat.

COMMENT

Evidence against the utilization of emulsified fat injected intravenously is the failure to observe alteration in the quality of depot fat (iodine and saponification numbers) following the injections and the failure to observe protein-sparing effects of intravenously injected fat in 9 of 11 dogs studied. Evidence suggesting limited utilization was afforded in some studies by the alteration of melting points in depot fats in the direction of the fat infused and the presence of nitrogen-sparing effects of infused fat in dog 500 (table 2).

Infusion of fat as performed in these studies was not without danger, since 9 of 24 dogs died as a result of the infusions. It would seem likely that the cause of death was primarily mechanical interference with function of the liver, lungs and kidneys. There appeared to be no means of predicting which animals would succumb to injections of fat and which would tolerate them. The size of an animal was of no importance in this connection. The surviving dogs appeared to be in good health and to gain weight. Tissues taken when they were killed, at various intervals later, were normal or showed decreased amounts of fat that had accumulated in sites previously described.

Dogs surviving infusions of demal emulsions appeared to be as vigorous as those surviving infusions of lecithin emulsions, and 3 of the 4 dogs gaining weight had been given demal emulsions. Five dogs that died after receiving demal emulsions showed in the liver, lungs, kidneys and spleen lipid globules relatively much larger than those seen in the tissues of 4 dogs that died after receiving lecithin emulsions. It is possible that demal emulsions apparently stable in vitro were less stable in vivo, perhaps as a result of their relative instability in the presence of electrolytes. The use of synthetic emulsifying agents might well be investigated further, since if a satisfactory one should be found it would have definite advantages over lecithin, i. e. known formula and greater ease in handling.

As stated previously, the advantages that would be afforded by successful intravenous administration of fat in addition to carbohydrate and casein digests would be in the high caloric value per unit volume and the administration of other possible essential factors in nutrition (unsaturated fatty acids). Present methods for the preparation of emulsions for such injections may be inadequate. Furthermore, little is known of the factors in the intestinal wall concerned with absorption of fat, and these factors are not operative when the fat is injected intravenously.

SUMMARY

Control dogs on a diet of commercial dog food of low fat content, 4 to 6 per cent, exhibited changes in the characteristics (iodine and saponification numbers) of the depot fat. Dogs receiving the same diet plus intravenous infusions of emulsified fat of appreciably different quality from dog fat did not exhibit sufficient differences from the control group in alteration of the iodine and saponification numbers to indicate appreciable physiologic storage of such infused fat. Changes in melting points of the depot fats in some of the animals given infusions, however, did suggest some storage of infused fat.

Protein-sparing effects were not demonstrable by intravenous injection of highly emulsified fat (except in 1 of 5 dogs), but such effects did result when comparable amounts of an emulsion were administered by mouth. This further indicated lack, or extreme limitation, of utilization of intravenously administered fat.

Histologic examination of tissues taken after infusions of fat showed increased fat in the liver, in macrophages in the spleen, in tubular epithelium of the kidneys and scattered sparsely in

capillaries and macrophages in the lungs. After administration of coarser or less stable emulsions there were large fat globules in sinuses in the liver, often in the Kupffer cells and in sinuses in the spleen, increased fat in the renal tubules and glomeruli and pulmonary capillaries loaded with fat. The foreign fat diminished with the passage of time. There was an increased amount of hemosiderin in macrophages mobilized in the regions of accumulation of foreign fat, especially in the spleen.

The infusions of fat produced severe secondary anemia in the dogs from which they recovered after the infusions were discontinued.

The infusions of fat were probably responsible for the deaths of 9 of 24 dogs; hence such infusions are not without appreciable danger. The surviving dogs appeared to maintain good health.

OSGOOD-SCHLATTER DISEASE

EDMOND UHRY JR., M.D.
NEW YORK

The early modern medical literature contains references to Osgood-Schlatter disease under one name or another (see, for instance, the review by Dunlop [1]). However, to Osgood [2] and to Schlatter [3] belongs the credit for crystallizing the present day understanding of the disorder as a clinical entity. In their original papers, both published in 1903, Osgood and Schlatter defended the idea that the condition is a manifestation of minor trauma at the site of insertion of the patellar ligament into the tibia, in the region of its tubercle. In addition, their papers contain considerable data on the anatomy and development of the structures involved. The subsequent literature on the subject, while abundant, deals mainly with clinical considerations and with problems of treatment. It largely lacks factual discussion of the pathologic anatomy of the condition.

Apparently, the disorder results from either functional abuse of or frank insult to the region in question at the time when its developing anatomic structure withstands most poorly the stress of its function. Clearly the disease is not to be included among the fractures and avulsions of the tibial tubercle resulting from *severe* trauma. In addition to describing the pathologic picture, on the basis of 23 pertinent specimens, and drawing inferences from these specimens as to pathogenesis, I plan to survey (on the foundation of clinical cases from our hospital) certain more general facts relevant to the understanding of Osgood-Schlatter disease. On the basis of these it will become clear that the original conception propounded by Osgood and by Schlatter, forty years ago, concerning the cause of this disease is fundamentally sound.

The work reported here was done in the Laboratory Division of the Hospital for Joint Diseases while the author held the Frauenthal Orthopedic Research Fellowship, prior to his entrance into the Medical Corps, A. U. S.

1. Dunlop, J.: The Adolescent Tibial Tubercle, Am. J. Orthop. Surg. **9**:313, 1912.

2. Osgood, R. B.: Lesions of the Tibial Tubercle Occurring During Adolescence, Boston M. & S. J. **148**:114, 1903.

3. Schlatter, C.: Verletzungen des schnabelförmigen Fortsatzes der oberen Tibiaepiphyse, Beitr. z. klin. Chir. **38**:874, 1903.

CLINICAL CONSIDERATIONS

The clinical statistical considerations presented here are based on 79 unselected cases from the records of the Hospital for Joint Diseases.[4] The records are not complete in all these cases, but they still permit certain generalizations about the clinical picture.

Table 1 groups these 79 cases by age of the subjects at the time of admission to the hospital or of registration in the outpatient department. It also shows the age at time of onset of the symptoms in 55 of these 79 cases, first for both sexes together and then for each sex separately.

TABLE 1.—*Age of Registration or Admission in 79 Cases and Age of Onset of Symptoms in 55 Cases, Charted by Year of Age*

Age in Years	When first Registered or Admitted	At Onset of Symptoms	At Onset of Symptoms in Females	At Onset of Symptoms in Males
8	..	2	2	..
9	..	..	..	..
10	2	4	3	1
11	8	12	3	9
12	18	14	..	14
13	16	13	1	12
14	12	4	..	4
15	15	4	..	4
16	2	..	..	..
17	..	..	..	..
18	..	..	..	..
19	1	1	..	1
20	..	..	..	..
21	2	1	..	1
22	2	..	..	..
23	..	..	..	..
24	1	..	..	..
Total	79	55	9	46

Specifically, table 1 shows that the onset of the symptoms was most frequently in the age period of 11 to 13 years and that symptoms most commonly reached a severity sufficient to make the patient seek medical care between the ages of 12 and 15. Furthermore, it seems clear that, as has also been found by many others, the

4. These 79 cases are by no means all of the cases of Osgood-Schlatter disease in the files of the hospital. Indeed, in 1935, C. J. Sutro and M. M. Pomeranz (Osgood-Schlatter's Disease, Arch. Surg. **31**:807 [Nov.] 1935) discussed the clinical and roentgenologic aspects of 106 cases drawn from the hospital files, and those were not all of the relevant cases even up to that time. The two groups of cases overlap somewhat, but many of the 79 cases reported here date from after 1935.

disease became manifest at an earlier age in the female than in the male patients, though the number of female patients forming the basis for this comparison is small. As to sex, males were definitely in the majority; there were 66 boys and only 13 girls.

In these cases the disease showed no predilection for one side of the body over the other. Specifically, the right apophysial region was the site of the lesion in 27 cases and the left in 25, while in an additional 24 cases there were bilateral lesions. (Three records failed to state which side was affected.) The group of cases previously reported from this hospital by Sutro and Pomeranz showed the same relatively even distribution. These observations are in disagreement with the general previous trend of opinion (see, for instance, Schlatter), according to which the condition occurs much more commonly on the right side than on the left.

The disorder usually appears in well developed and active subjects, who may give a history of injury, although many do not associate any such occurrence with the appearance of the disease. As the data show, the disorder may be bilateral, but is more commonly unilateral. The severity, duration and degree of incapacitation vary widely from case to case. In the majority of instances, the course of the disorder is limited by the somewhat early closure of the apophysial cartilage plate, although in a small number of cases, in which there is delay in apophysial closure, the symptoms (pain or tenderness, limitation of function, etc.) may persist well into the third decade.

Definite relevant antecedent injury was reported in a considerable proportion of the cases, but the data on this point appear to be incomplete. The trauma usually consisted of either a fall or a collision, but in not a single case had it led to gross fracture of the tibia or of any other bone. In the majority of cases pain was present on the application of hard local pressure, or even when the patient was at rest or engaged in extremely mild activity. Also in a great number of instances enlargement of the part was palpable. The histories sometimes recorded fluctuation of the swelling, increased local heat and even effusion into the knee joint. The disorder was not found objectively to have affected the stability of the knee, and in the few cases in which there was limitation of motion, this limitation was minor.

Review of the roentgenograms taken in our cases showed, in the first place, more or less fuzziness of the border shadow of the tibial tubercle. Sometimes it also appeared that the tongue had been pried slightly upward, its prominence being increased and the space between it and the underlying tibia being abnormally wide. Occasionally, what appeared to be a shadow of a free bony fragment could be observed lying in the ligament above and in front of the tubercle. In some instances, in which roentgenograms of serial sections were made after removal of the region en masse, the evidence of loss of local definition in the bone-cartilage or bone-ligament border shadows was even more clearly apparent. In some of them the translucent or transparent shadow of a scar could be seen interposed between the bulk of the osseous apophysis and a small shadow of a flake of bone, actually avulsed forward in the process of separation. The general softness of the normal roentgen shadow of the growth zone (posterior surface of the apophysial plate) tended to obscure the changes when they occurred in that region.

The various routine clinical laboratory examinations yielded no pertinent information so far as the local lesion was concerned.

ANATOMIC CONSIDERATIONS

Before consideration of the pathologic changes in cases of Osgood-Schlatter disease, a few orienting remarks on the anatomic features and development of this region seem appropriate.

The tibial tubercle develops from a tongue of cartilage growing (at some time in early childhood) from the upper tibial epiphysis over the anterior face of the tibial metaphysis. In this cartilaginous tongue an ossification center develops, which is usually single, though it may be multiple and otherwise irregular. The ages cited for the appearance of the ossification center for the tubercle range between 8 and 15 years, but, probably, no such range exists in fact. Indeed, it seems that in most instances the ossification center appears at just about 11 years. Union of the apophysis with the epiphysis occurs a few months after the appearance of the apophysial ossification center. By about the fourteenth year of life, the apophysis presents itself roentgenographically as a sort of beak or tongue. Fusion of the beak with the shaft of the tibia frequently lags behind union of the remainder of the upper epiphysial complex of the tibia with the shaft. In the majority of instances, the beak unites with the shaft at the age of 18 years. It may unite somewhat before that age, but normally the union is rarely delayed beyond the age of 19.

During the formative stage and before fusion with the shaft of the tibia, the tibial apophysis is separated from the tibial shaft by an apophysial cartilage plate. At the anterior end of this plate, the patellar ligament is invaginated between the apophysial beak and the tibia for a

millimeter or two. The attachment of the ligament to the apophysis is characterized by investment of the bone by heavy ligamentous collagenous fibers, which interlock with those of the bony matrix of the part. (Occasionally one finds calcification of the ligamentous fibers at the bony junction without formation of new bone.)

The attachment of the patellar retinacula to the oblique ridges of the tibia, which curve upward and backward on either side, extending from the tubercle to the condyles, was described by Terry [5] as follows: The lateral and medial patellar retinacula have central portions attached to the patella and arising from the rectus tendon. These pass over into the patellar ligament. The two thinner, less axial portions attach to the tibia along the oblique ridges as far from the midline as the site of attachment of the medial and lateral collateral ligaments. The patellar ligament, a continuation of the central part of the quadriceps tendon below the patella, is attached to the tibial tubercle and the upper part of the tibial crest in a somewhat oblique fashion, as the attachment is longer on the lateral side. Medially and laterally, from the sagittal plane of the tibia on either side, this ligament is continuous with the retinacula.

It is important to note that the collateral attachments of the patellar complex are able to preserve the greater part of the extension power of the knee, even though the attachment of the patellar ligament to the tibial tubercle has been invalidated. Indeed, in the event of complete separation in that region, upward displacement of the patellar insertion or of any avulsed fragments of bone is sharply limited. Osgood demonstrated the efficiency of the patellar collaterals and stated that the separation of the tibial tubercle fragment from the tibia in the cadaver, in which transection had been undertaken, was only ¼ inch (0.6 cm.) and that extension at the knee was not impaired.

PATHOLOGIC CHANGES

This part of the study is based, as noted, on examination of 23 adequate specimens [6] taken from 20 subjects. From the notes dictated at the time of operation in these cases, I gathered that in general the area of the tibial tubercle appeared injected and there was increased vascularity of the overlying soft tissues. Furthermore, in some cases, there was increased mobility of the tubercle, since when the latter was firmly grasped, the tongue could be forcibly moved from side to side. There was never any evidence of true fragmentation of the tubercle. Occasionally a focus of intraligamentous ossification was found.

To some extent on the basis of gross examination, but mainly on the basis of microscopic study, it is evident that the fundamental pathologic change in Osgood-Schlatter disease is separation of two or more structures comprising the tibial tubercle complex, with the interposition of scar tissue between them. This alteration may be found on any one or more of the interfaces formed between the patellar ligament, apophysis, apophysial cartilage plate and tibial metaphysis. In none of the specimens was there any evidence that a local disease process antedated the separation. At the site or sites of separation I characteristically observed scar tissue or even callus. In addition, I occasionally noted the presence of one or more small fragments of bone in the ligament in the general vicinity of its attachment.

In 13 of the 23 specimens, the scar-callus was seen between the patellar ligament and the apophysis—that is, on the anterior face of the tibial tubercle (fig. 1 *A* and *B*). In 3 others it was present on the posterior surface of the apophysial cartilage plate (fig. 1 *C*). In 4 others it was in the zone of growth, at the junction between the columns of proliferating cartilage and the newly formed endochondral bone on the posterior side of the apophysial plate. In each of the remaining 3 specimens a double lesion was present. In 2 of these separation had occurred in relation to both the anterior and the posterior surface of the apophysis—that is, at the apophysial-ligamentous surface on the one hand and at the apophysis–apophysial cartilage surface on the other (fig. 2 *A*). In 1 of these 3 specimens both the anterior apophysial surface and the growth zone were involved and a fracture had occurred between the tip and the rest of the beak of the apophysis, the fragments being separated by a pseudarthrosis (fig. 2 *B*). In another of them there had apparently been an incomplete fracture near the very tip of the apophysis, at which site a small cystic area, resulting apparently from liquefaction of organizing hemorrhage, was seen (fig. 2 *C*).

As specimen after specimen was examined, evidence accumulated that early in the evolution of the pathologic picture organization of hemorrhage had occurred. This hemorrhage had apparently been released when the interfaces between the bone and ligament or the bone and

5. Terry, in Morris, H.: Human Anatomy, edited by C. M. Jackson, ed. 9, Philadelphia, P. Blakiston's Son & Co., 1933, p. 352.

6. Of these, 16 (from 14 subjects) came from the clinical series of 79 cases from the Hospital for Joint Diseases. The other 7 (from 6 subjects) came from the collection of pathologic material preserved by the late Viennese pathologist Jacob Erdheim and now housed in the laboratory of this hospital.

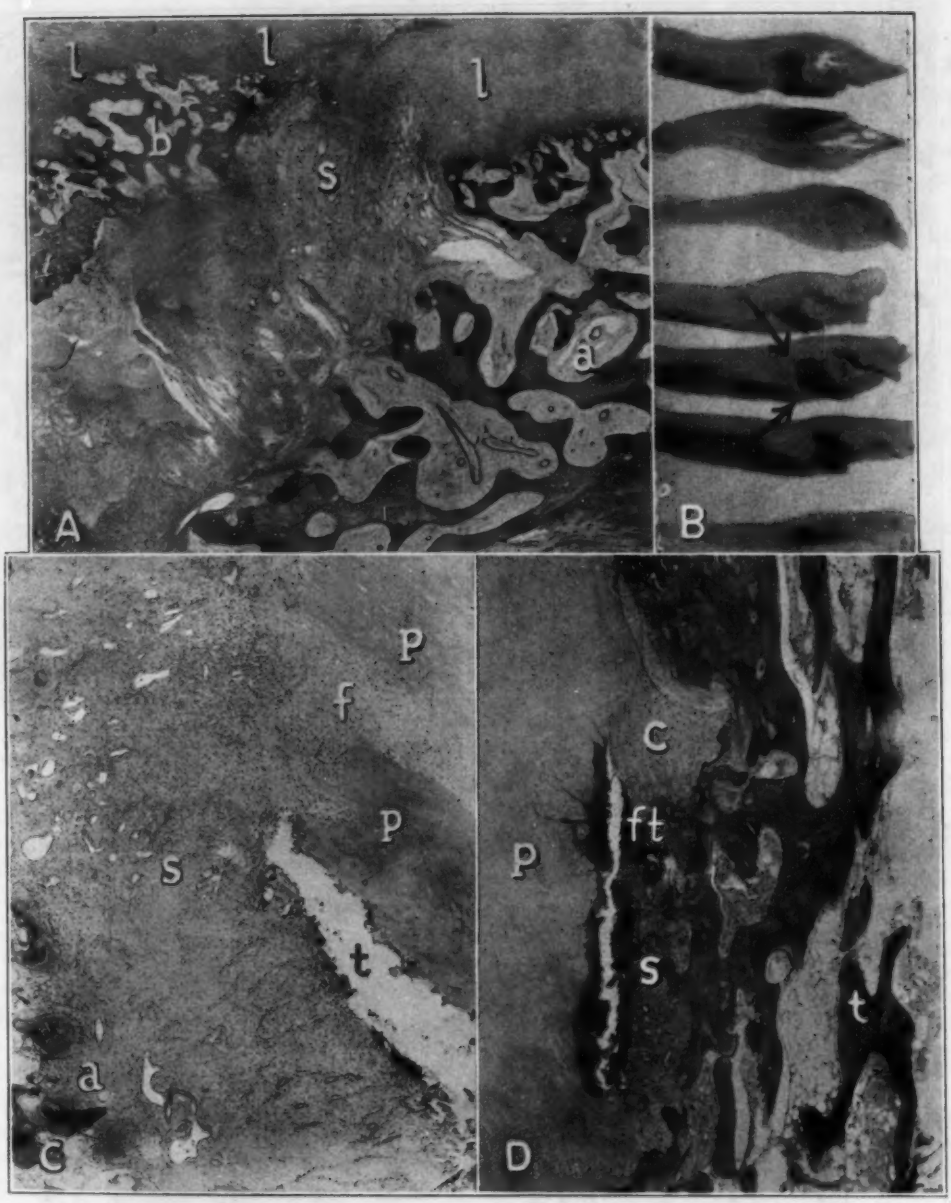


Fig. 1.—Scars of separation at various interfaces. *A*, photomicrograph (× 10) showing a scar (*s*) on the anterior face of the apophysis (*a*); note also a small fragment of bone (*b*) which has been carried forward with the ligament (*l*). The scar shows moderate vascularity and fibrous organization, and the appearance of the repair tissue also suggests that this tissue did not develop in consequence of a single trauma. *B*, roentgenogram of a sectioned gross specimen; the piece lying between the arrows represents the slice from which the section shown in *A* was prepared. *C*, photomicrograph (× 25) demonstrating the conditions in another case, in which the scar (*s*) lies in the interface between the apophysis (*a*) and the apophysial plate (*p*). The scar also extends through the plate itself (*f*). A fresh separation has occurred between the scar and the plate (*t*). *D*, photomicrograph (× 25) showing a scar (*s*) at the growth zone, on the posterior surface of the apophysial cartilage plate (*p*). Sparse columns of cartilage cells (*c*) indicate a slow rate of growth of bone. The metaphysial trabeculae (*t*) are thick. A fresh tear (*ft*) without hemorrhage is also shown.

Fig. 2.—A few unusual variations of the lesion. *A*, photomicrograph (× 25) from a case in which separation (and scar) has occurred at the anterior surface of the tip of the apophysial beak (*sa*) and also along the posterior surface of the entire beak (*sp*). There is a fracture line (*fl*) filled in with a young scar between the apophysial tip (*at*) and the apophysial body (*ab*). *B*, photomicrograph (× 25) showing a fracture of the tip of the apophysis, with pseudarthrosis. The tip (*at*) has broken from the body of the apophysis (*ab*), and a scar (*s*) is present between them. Scars on the anterior and posterior surfaces (*sa* and *sp*) are also shown. The pseudarthral space (*ps*) has a thin connective tissue lining, and the scar about the latter is condensed. *C*, photomicrograph (× 10) showing a cystified area (*c*) between the apophysial tip (*at*) and the apophysial beak (*ab*) in a specimen in which the anterior surface of the apophysis is involved and an incomplete fracture of the tip has occurred.

cartilage had been disrupted. Indeed, in some specimens free hemorrhage and hemosiderin pigment were still seen in the organizing reactive connective tissue. In most of the specimens, however, at the time of examination, the organization of the hemorrhage was already further advanced and the tissue representing the scar-callus was more or less mature connective tissue of moderate cellularity and moderate to extreme vascularity (fig. 3 *A*).

Along the line of contact between the scar and the bone, some osteoblasts, along with osteoclasts in Howship's lacunas, were observed. In many instances, fragments of necrotic bone undergoing resorption were seen in the connective tissue scar. In other specimens, trabeculae of new bone were being formed in the scar-callus, after the manner of fiber-callus (fig. 3 *B* and C). When avulsion, particularly of the patellar ligament, carried a fragment of bone forward with it, that bone became necrotic and then underwent replacement by creeping substitution. Wherever the laceration was revealed by even a minor fracture through the bone, the osseous tissue bordering on the area was observed to be partly or completely necrotic and also undergoing creeping substitution. In the specimen presenting pseudarthrosis, an ordinary pseudarthral space had formed between condensations of the scar, which completely surrounded and lined this space. In miniature, the picture corresponded to that typical of nonunion with pseudarthrosis in larger bony structures. Furthermore, the apophysis showed fibrosis, and in some places scarring, of its marrow. Occasionally, a sparse intermingling of lymphocytes was to be seen, but there was no evidence of specific or nonspecific inflammation.

Adequate control material was examined. The material consisted of areas from normal, rachitic, tuberculous and osteomalacic tibial tubercles. In addition, control material from cases of Perthe's disease of the femoral capital epiphysis and from other instances of so-called osteochondritis (epiphysial aseptic necrosis) was examined. It should be emphasized that in none of the cases of Osgood-Schlatter disease was there anything in the anatomic picture to indicate that that disorder belongs with the so-called osteochondritides or can be related pathogenetically with any specific or nonspecific inflammatory condition.

COMMENT

If one surveys the descriptions of the pathologic changes [7] given in the literature on Osgood-Schlatter disease, one finds that, though the alterations have been variously interpreted, the findings themselves, as reported in these descriptions, are consistent with interpretation of the condition as a repair reaction to trauma.

The explanation of the special age of appearance of the lesion is related to the ontogenesis and the anatomic peculiarities of the tibial apophysis. Specifically, ossification in the cartilaginous precursor of this apophysis sets in at about 11 years, temporarily diminishing the resiliency of the area's response to functional demands, which happen to be particularly great in this period. After ossification of the apophysis is complete (at about 14 years), and especially after the apophysis has fused with the shaft of the tibia (at about 18 years), the region is more resistant to functional and traumatic stress. Correspondingly, in a large number of clinically and roentgenographically verified cases there are only minor lesions of brief duration. On the other hand, a considerable number of lesions persist and remain active even beyond the normal age of fusion of the apophysis with the tibia. It has been held, for instance by Brandes,[8] that the persistence of the disorder during early adulthood is related to delay in fusion of the apophysis with the tibia in subjects in whom the condition was already present during adolescence.

7. Anardi, T.: Contributo allo studio della malattia di Osgood-Schlatter, Chir. d. org. di movimento **12**: 187, 1928. Asada, T., and Kato, S.: Zur Aetiologie der sogenannten Schlatterschen Krankheit, Ztschr. f. orthop. Chir. **48**:191, 1927. von Brandis, H. J.: Zur Frage der Schlatterschen Krankheit, Ztschr. f. orthop. Chir. **48**:239, 1927. Cole, J. P.: Study of Osgood-Schlatter's Disease, Surg., Gynec. & Obst. **65**:55, 1937. Giuliani, G.: Malattie scheletriche della crescenza. (Morbo del 2° metatarseo di Kohler. Morbo di Osgood-Schlatter), Chir. d. org. di movimento **17**:105, 1932. Harbin, M., in Ghormley, R. K.: Orthopedic Surgery, New York, Thos. Nelson & Sons, 1938, p. 248. Hermeto, S., Jr.: A affeccao de Osgood-Schlatter como anomalia de ossificacao da tuberosidade anterior da tibia, Rev. Assoc. paulista de med. **6**:61, 1935. Hörbst, L.: Mikroskopische Befunde bei der sogenannten Schlatter-Osgoodschen Erkrankung (apophysitis tibiae) und bei Osteochondritis des Mondbeines, Arch. f. orthop. u. Unfall-Chir. **33**:229, 1933. King, E. S. J.: Localized Rarefying Conditions of Bone, Baltimore, William Wood & Company, 1935, pp. 88, 90 and 189-203. McIlhenny, P. A.: Avulsion of the Tibial Tubercle (Osgood-Schlatter's Disease), New Orleans M. & S. J. **88**:636, 1936. Quintero Fossas, J. M.: Dos casos de enfermedad de Osgood-Schlatter, Rev. méd. cubana **45**: 396, 1934. Sandberg, M., and Marín Moreno, N.: Apofisitis tibial anterior o enfermedad de Osgood-Schlatter, Semana méd. **2**:1917, 1932. Stracker, O.: Zur Histologie der Schlatterschen Erkrankung, Ztschr. f. orthop. Chir. **58**:242, 1932. Walter, H.: Die Entstehung der lokalen Malacien (Osteochondritis dissecans, Perthes-, Köhler-, Schlattersche Krankheit und andere verwandte Prozesse), Arch. f. orthop. u. Unfall-Chir. **25**:557, 1927.

8. Brandes, M.: Der Schlattersche Symptomenkomplex beim Erwachsenen, München. med. Wchnschr. **74**:1830, 1927.

A word should be said about fractures of the tibial tubercle in comparison with Osgood-Schlatter disease. Direct trauma and the indirect trauma of sudden, massive muscular contraction against unusual resistance do cause the tearing out of the attachment of the patellar ligament along with more or less of the underlying tubercle, with damage to the collateral structures. In some cases a part of the tibial plateau in the adult, or of the superior tibial epiphysis in younger subjects, may be torn along. The condition of fracture has been discussed in the early literature, and many of the original descriptions are included in a review by Gaudier and Bouret.[9] in 1905. This lesion is massive and is not limited to the adolescent period or by the state or existence of the apophysial plate. The differentiation of this condition from Osgood-Schlatter disease, in spite of its many gross similarities, was well understood by Osgood and by Schlatter.

Trauma is the causative factor most frequently mentioned in connection with Osgood-Schlatter disease. However, a large body of the literature, while recognizing the important role of trauma in the immediate causation of the disorder, defends the idea that the trauma acts on a tibial tubercle area which is constitutionally inferior or is already otherwise diseased. I am among those who reject the idea of these predisposing influences in this disorder and inculpate trauma alone.

The pathogenesis of Osgood-Schlatter disease on the basis of trauma alone can best be elucidated by consideration of the mechanical factors involved. The structure of the region of the tibial tubercle is laminated. The patellar ligament overlies the apophysis, which in turn is in contact with the apophysial plate, which finally, through the intermediation of its growth zone, is in contact with the tibial metaphysis. The bonds between the single elements in any such structure constitute weak points. Separation can occur cleanly at any interface between laminas, but if, locally, the bond is stronger than the substance of one of the laminas, fragments of a lamina may be carried away on separation. This mechanism offers a background for the tearing off of flakes of bone in the specimens in which fragments of free aseptically necrotic bone were seen, usually in the patellar ligament.

In addition, the attachment of the patellar ligament at its insertion is mechanically inadequate. The principal point of application of force, although well supported by less taut collateral structures, is extremely small, while the muscle acting, the quadriceps, is the largest in the body (Cole[7]). The pull of the muscle is always in an upward direction, in the plane of the anterior tibial crest. This direction persists, in its relation to the tibia, for any angle of flexion at the knee. This is so because the patellar insertion is located well below the axis of the hingelike motion of the knee joint and because the infrapatellar fat pad acts as a block to prevent the ligament from imposing directly on the tibial epiphysis when the quadriceps acts on the flexed knee. Furthermore, this line of force runs against the grain established by the planes of lamination of the tibial tubercle complex.

It is a familiar fact that when heavy or adherent objects are pulled along a board floor in the direction of the grain of the boards, splinters, which are the result of fractures of wood fibers, are more likely to be raised than when the stress is applied across the grain of the wood. Under the force of the quadriceps muscle there is a similar tendency for the tibial tubercle to be pried upward. The part is vulnerable to such prying action by virtue of the direction of the grain, as determined by the anteroinferior projection of the tibial tubercle and the similar direction of the planes of the interfaces involved in the tubercle complex. However, since retroapophysial separations, such as would occur with elevation of the tubercle, are in the minority, this can be only one of the factors at work.

In view of the occurrence of the majority of separations at the anterior face of the apophysis, it may be suggested that the placement of all of the interfaces which may be involved (particularly that of the ligamentous-apophysial face) in planes very nearly parallel to the plane of the pull of the muscle favors a slipping of the parts and a beginning separation. In addition, the disparity between the size of the attachment and

9. Gaudier, and Bouret, A. O.: De l'arrachement de la tubérosité antérieure du tibia, Rev. de chir. **32**: 305, 1905.

Fig. 3.—An early and a later phase in the production of the scar. *A*, photomicrograph (× 60) showing a young scar (*s*) with a scattered round cell infiltration and young but well organized vascular channels (*v*). An area of hemorrhage (*h*) can be seen below. *B*, roentgenogram of a sectioned gross specimen; the piece lying between the areas represents the slice from which the section shown in *A* was prepared. *C*, photomicrograph (× 60) showing a later phase, with early callus. Fragments of necrotic bone (*b*) can be seen undergoing lacunar resorption, as are new fiber bone (*fb*) and osteoid tissue (*ot*). The blood channels (*v*) are numerous.

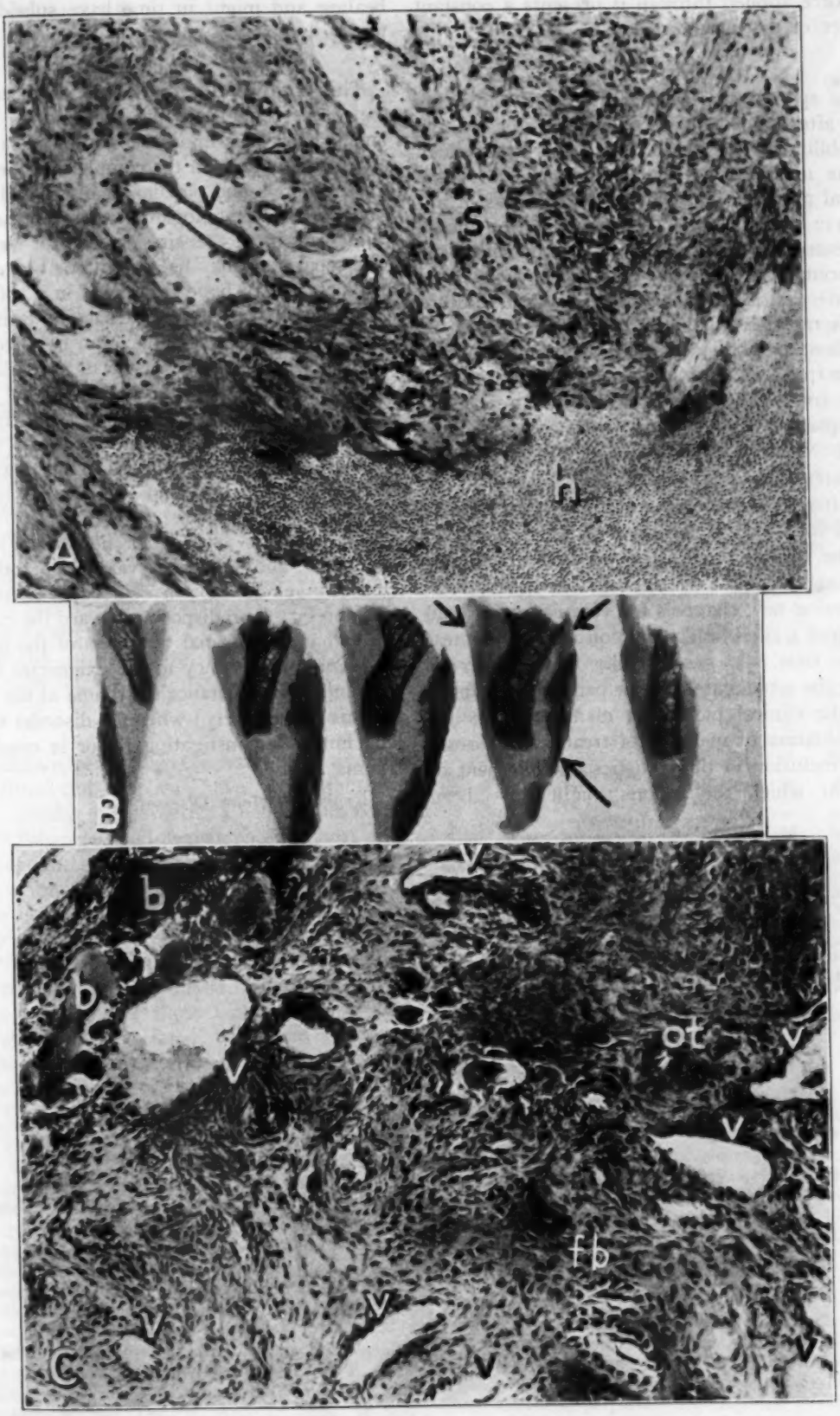


Figure 3

(See legend on opposite page)

the force applied through it presents a constant danger of disruption.

TREATMENT

The spontaneous healing that occurs in many cases after inadequate immobilization, or even no immobilization at all, indicates that many small lesions must heal without any support to the natural processes of repair. Nevertheless, it appears to me that, in general, the condition should be treated as solutions of continuity with little displacement are treated elsewhere in the skeletal system—that is, by early immobilization. Failure of this measure justifiably leads the surgeon to the use of methods indicated in cases of nonunion of true fractures, such as excision of useless fragments, freshening of apposing surfaces, reposition of displaced structures and renewed immobilization. Needling of the apophysial plate to speed its destruction and closure will not attack the more frequent site of involvement, the anterior face of the tubercle. Drilling, on the assumption that the disorder represents an osteochondritis, is unwarranted as a rule, and its use as a method of favoring new channels for vascularization and healing of a site of old nonunion is under contest at this time. In general, the impossibility of gaging the actual extent of the pathologic changes from the clinical picture in many cases clouds the evaluation of methods of treatment, because of the inclusion in the statistics on treatment of cases in which the lesions might have been healing and might in time have subsided spontaneously.

CONCLUSIONS

This study of Osgood-Schlatter disease leads me to the conclusion that the disorder develops on the basis of a minor separation of structures, one from another, in the complex comprising the tibial tubercle and patellar ligament and that the characteristic pathologic changes represent scar-callus repair at the site or sites of separation. The separation may be a clean one or may entail the inclusion of bone fragments in a softer part, as it is torn free. Any interface or combination of interfaces in the complex can be affected, but the majority of separations occur at the ligament-apophysis face, the anterior apophysial surface. Occasionally, a fracture of the very tip of the tubercle is also found, with healing or with the formation of a pseudarthrosis, in association with the processes of repair of the disruptions at the interfaces.

Inflammation (specific or nonspecific), osteochondritis, and endocrine, vascular or other specific changes are not in evidence. There seems to be no factor predisposing toward the condition other than the normal weakness of the part and its relative inadequacy to the exigencies of function and poor resistance to trauma at the time of life (usually puberty) when the disorder appears. The immediate instigating factor is consistently trauma.

Hospital for Joint Diseases.

INTERSTITIAL CELL TUMORS OF THE TESTIS

REPORT OF THREE NEW CASES

EARL F. NATION, M.D.
PASADENA
AND
HUGH A. EDMONDSON, M.D., AND ROY W. HAMMACK, M.D.
LOS ANGELES

The interstitial cells of the testicle, which were first described by Leydig [1] in 1850, may rarely give rise to tumors, some of which are accompanied with endocrine changes. These cells have been regarded generally as the primary source of androgen. The study of such tumors is of interest, therefore, and may contribute to the knowledge of the normal endocrine physiology of the testis.

This paper is concerned primarily with a review of the hormonal manifestations described in the previously reported cases of interstitial cell tumor and a report of 3 new cases, in which the patients were adults, one of whom had gynecomastia. In addition, we have elaborated certain criteria for the recognition of these tumors.

LITERATURE

Several comprehensive reviews of the literature of interstitial cell neoplasia have been published recently, notably by Jemerin,[2] Fialho [3] and Warren and Olshausen.[4] However, these writers and others have disagreed concerning the genuineness of various reported cases, and each of them has failed to note some cases about which there can be little doubt. The reports of interstitial cell tumors which the majority of reviewers have considered authentic are listed in tables 1 and 2. The former includes those instances in which there were no associated endocrine changes, while the latter presents all cases in which the patients had such manifestations.

In addition to the tabulated cases of interstitial cell tumor, 7 others have been reported, but in each instance either there are insufficient data for definite classification or the original report is not available.[5] Several other authors who have reported testicular tumors believed to be of interstitial cell origin are now thought to have been mistaken.[6] In none of these doubt-

TABLE 1.—*Reports of Patients with Interstitial Cell Tumors with No Associated Endocrine Disturbances*

Author	Year of Report	Age of Patient, Yr.	Benign or Malignant
Chevassu: Thesis, Paris, no. 193, 1906.	1906	27	Benign
Kaufmann: Verhandl. d. deutsch. path. Gesellsch. **11**: 237, 1907	1907	30	Benign
Kaufmann: Deutsche med. Wehnschr. **34**: 808, 1908	1908	34	Benign
Masson and Sencert [8]	1923	62	Malignant
de Josselin de Jong [11]	1926	42	Malignant
Pana: Urol. & Cutan. Rev. **35**: 561, 1931	1931	16	Benign
Rigoletti: Arch. per le sc. med. **61**: 557, 1936	1936	20	Benign
Jemerin [2]	1937	35	Benign
Braun: Virchows Arch. f. path. Anat. **304**: 106, 1939	1939	45	Benign
Fialho [3]	1941	44	Benign
Masson,[9] Venning [10]	1942	32	Malignant
Warren and Olshausen [4]	1943	30	Benign
Bonser and Hawksley,[7] case 1	1943	49	Benign
Bonser and Hawksley,[7] case 2	1943	31	Benign
Sharnoff and Lisa [12]	1943	67	Malignant
Nation, Edmondson and Hammack case 1	1944	34	Benign
Nation, Edmondson and Hammack case 3	1944	82	Malignant

From the St. Luke Hospital, Pasadena, the Department of Urology and the Laboratory of the Los Angeles County General Hospital and the Department of Pathology of the School of Medicine of the University of Southern California.

1. Leydig, F.: Zur Anatomie der männlicher Geschlechtsorgane und Analdrüsen der Saugertiere, Ztschr. f. wissensch. Zool. **2**:1, 1850.

2. Jemerin, E. E.: Hyperplasia and Neoplasia of the Interstitial Cells of the Testicle, Arch. Surg. **35**: 967 (Nov.) 1937.

3. Fialho, A.: Sobre un caso de tumôr de celulas de Leydig, Rev. brasil. de cir. **10**:53, 1941.

4. Warren, S., and Olshausen, K. W.: Interstitial Cell Growth of the Testicle, Am. J. Path. **19**:307, 1943.

5. Peppere: Ghiandole a secrezione interna, in Foà, P.: Trattato di anatomia patologica, Turin, Union tipografico-editrice torinese, 1922, vol. 8, p. 266. Slanina, P.: Vzachny nador varlette slozeny z. bunek interstitialnich, Casop. lék. česk. **69**:935, 1930. Ciceri, C.: Tumors of the Testicle, abstracted, Urol. & Cutan. Rev. **37**:648, 1933. Pitrolffy-Szabó, B.: Die bösartigen Hodengeschwülste, Ztschr. f. Urol. **31**:823, 1937. Delitala, cited by Fialho.[3] Schaany, cited by Fialho.[3] Ogata and Kaneko, cited by Fialho.[3]

6. Waldeyer, W.: Die Entwickelung der Carcinome, Virchows Arch. f. path. Anat. **55**:67, 1872. Hansemann, D.: Ueber die sogenanten Zwischenzellen des Hodens und deren Bedeutung bei pathologischen Veränderungen, ibid. **142**:538, 1895. Durck, H.: Ueber die Zwischenzellenhyperplasie des Hodens, Verhandl. d.

(Footnote continued on next page)

ful or unacceptable cases did the patient have any reported hormonal changes.

As will be seen in table 1, the youngest patient not having hormonal disturbances was 16 years of age (this tumor was found incidentally, at autopsy) and the oldest was 82. Ten of these 16 adult patients (63 per cent) were between 30 and 45 years of age. Five (19 per cent) of the tumors were definitely malignant. Bonser and Hawksley [7] reported 2 tumors which they considered malignant; however, we believe that they should be classed with the benign tumors. Metastases appeared in the patient described by Masson and Sencert [8] after four years and in the patient described by Masson [9] and Venning [10] after nine years. The malignant interstitial cell tumor reported by de Josselin de Jong [11] occurred in an undescended testis of an internally masculine pseudohermaphrodite. Some doubt has been expressed about the true nature of this tumor because of the extensive necrosis present. No metastases from the testicular tumor were found in the patient described by Sharnoff and Lisa.[12] The fifth malignant tumor is reported in our case 3.

Of the patients who had endocrine disturbances (table 2), the oldest was 42 and the youngest 5 years of age. All of the tumors in these patients were benign. The only endocrine change developing after puberty was gynecomastia, which occurred in 3 patients.

TABLE 2.—*Reports of Patients with Interstitial Cell Tumors and Endocrine Disturbances*

Author	Year of Report	Age of Patient, Yr.	Tumor: Benign or Malignant	Tumor: Duration, Yr.	Endocrine Disturbances	Effect of Orchidectomy
Sacchi: Riv. sper. di freniat. **21**:149, 1895	1895	9	Benign	4	Puberty at the age of 5½ years; hair on body and face, and erotic manifestations	All changes regressed except hair on lip and skeletal and muscular development
Monaschkin: Ztschr. f. Urol. **20**:8, 1926	1926	30	Benign	8	Bilateral gynecomastia, and atrophy of the uninvolved testis	Right orchidectomy and mastectomy followed by regression of left breast and enlargement of testis
Rowlands and Nicholson: Guy's Hosp. Rep. **79**:401, 1929	1929	9	Benign	3	Precocious bodily and sexual development	No regression
Stewart, Bell and Roehlke: Am. J. Cancer **26**:144, 1936	1936	5	Benign	1	Precocious growth of genitalia and pubic hair	All changes regressed
Budd: Am. J. Path. **13**:660, 1937	1937	42	Benign	½	Bilateral gynecomastia	Regression
Hunt and Budd: J. Urol. **42**:1242, 1939	1939	..	.....	..		
Somerford [14]	1941	11	Benign	6	Macrogenitosomia	No regression after 18 months
Huffman: J. Urol. **45**:692, 1941	1941	6	Benign	2	Growth of genitalia, breasts and pubic hair	Genitalia smaller; no regression of pubic hair or breasts
Werner and others: J. Clin. Endocrinol. **2**:527, 1942	1942	6	Benign	1	Precocious sexual, bodily and skeletal development	Beginning regression 3½ months after orchidectomy
Nation, Edmondson and Hammack, case 2	1944	30	Benign	2	Bilateral gynecomastia	No regression after 3 years

Each of the 6 tumors occurring in children was first noticed or manifested during the fourth or fifth year of life. All of the latter patients had precocious bodily and sexual development. After orchidectomy was performed the changes regressed entirely in 2 patients, partially in 2 others and not at all in the remaining 2. There was regression of gynecomastia in 2 of the adults and no regression in 1. There seemed to be no correlation between the duration of the tumor and the regression of the hormonal changes.

deutsch. path. Gesellsch. **11**:130, 1907. Stoppato, U.: Ueber Zwischenzellentumoren des Hodens, Beitr. z. path. Anat. u. z. allg. Path. **50**:113, 1911. Villata, G.: Di un tumore del testicolo di grandi cellule rotonde e di tessuto interstiziale, Arch. per le sc. med. **52**:28, 1928.

7. Bonser, G. M., and Hawksley, L. M.: Two Cases of Interstitial-Cell Tumour of the Human Testis, J. Path. & Bact. **55**:295, 1943.

8. Masson, P., and Sencert, L.: Cancer des cellules interstitielles, Bull. Assoc. franç. p. l'étude du cancer **12**:555, 1923.

9. Masson, P.: Tumeur maligne des cellules de Leydig, Rev. canad. de biol. **1**:570, 1942.

10. Venning, E. H.: Étude hormonale sur un cas de tumeur interstitielle du testicule, Rev. canad. de biol. **1**:571, 1942.

11. de Josselin de Jong, R.: Ein Fall von Zwischenzellengeschwulst in einen ektopischen Hoden bei Pseudohermaphroditismus masculinus internus, Frankfurt. Ztschr. f. Path. **34**:420, 1926.

12. Sharnoff, J. G., and Lisa, J. R.: Malignant Tumor of the Interstitial Cells of the Testis with Prostatic Carcinoma, J. Urol. **50**:471, 1943.

REPORT OF CASES

CASE 1.—P. M., a 34 year old Caucasian man, a clerk, was seen on Feb. 21, 1942 because of a lump in the right testis, which had been discovered by a physician one month before. There were no symptoms, and the patient's past health had been excellent. There was no history of testicular disease or injury. The patient had been married for twelve years but had no children. Libido and potency were considered to be average. Physical examination revealed no abnormalities except a firm, nontender, nodular tumor, 2 cm. in diameter, in the upper pole of the right testis. The prostatic fluid was normal but contained no spermatozoa. Laboratory examinations, including roentgenographic study of the chest, contributed no significant information. With the patient under spinal anesthesia, orchidectomy on the right side was performed, at St. Luke Hospital (E. F. N.).

Fig. 1 (case 1).—Rounded group of tumor cells showing relationship to connective tissue stroma. (× 50).

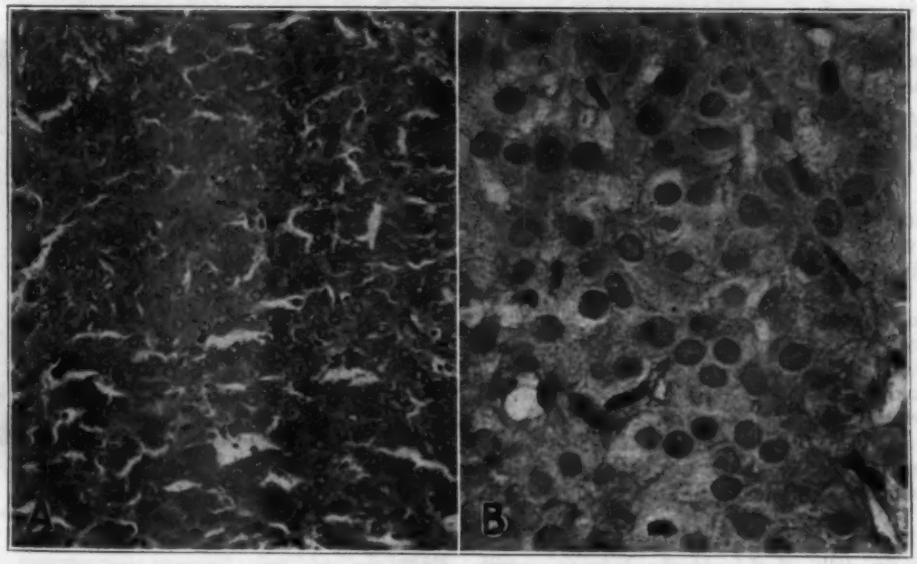


Fig. 2 (case 1).—*A*, tumor cells with round to oval nuclei containing eccentric nucleoli. (× 150). *B*, high magnification showing cellular details; note the mitotic figure near the lower margin. (× 450).

Six months after the operation the patient's seminal fluid contained only an occasional sperm. One and one-half years after orchidectomy the patient remained free of symptoms and exhibited no evidence of metastases.

Gross Appearance of Specimens.—Specimen *A* consisted of a fairly well circumscribed mass of tumor, 1.8 to 2 cm. in its greatest diameter. The external surface was slightly nodular, and there appeared to be a fairly definite capsule around the tumor. The cut surface was light brown to yellow-brown, and thin fibrous connective tissue septums were seen throughout. The brown tissue between the septums was rather soft.

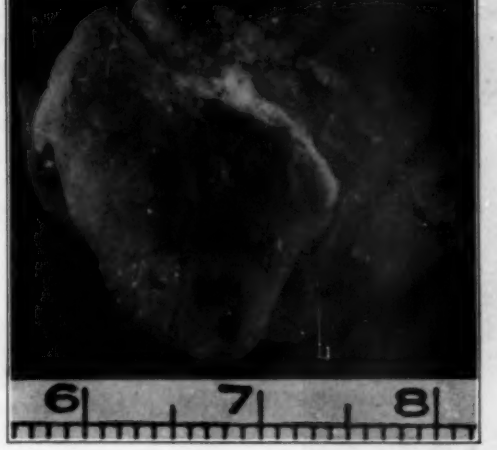


Fig. 3 (case 2).—Nodular tumor of testis with fibrous capsule. (Size indicated by the metric scale.)

Specimen *B* consisted of the testicle, the epididymis and a segment of the vas deferens. The testis measured 5.5 by 3.5 by 2 cm. The surgical incision from which specimen *A* was taken appeared in the tunica albuginea. Evidence of a small amount of hemorrhage was present around this incision, but no remnants of tumor were seen. No pathologic changes were seen in the epididymis, vas deferens or vessels.

Microscopic Appearance.—Sections of the tumor stained with hematoxylin and eosin disclosed it to be composed of round to irregular groups of cells resembling interstitial cells, separated by strands of relatively acellular and partially hyalinized connective tissue, in which there were a moderate number of blood vessels (fig. 1). Some of these groups of tumor cells were of considerable size, and into these large groups a fine network of stroma extended. The interstitial-like cells varied to some degree in appearance; the nuclei were oval to round and moderately hyperchromatic and contained one or more nucleoli. As in normal interstitial cells, many of the nucleoli were eccentric (fig. 2*A*).[13] Many of the nucleoli were multiple and small and probably are best described as having a punctate appearance. Mitotic figures were rare (fig. 2*B*). The cytoplasm of the cells was filled with fine, pink-staining granules, variable in number. In the cells of the older and more central portions of the tumor these granules were tightly packed, while in the cells of the peripheral portions they were fewer in number and the cytoplasm had a looser texture. Only an occasional cell contained lipochrome. No Reinke crystals were seen. In some areas the cell borders were indistinguishable, while in other areas they were sharp and clearcut. Between some of the cells there were large vacuolar spaces which probably represented both areas of intercellular edema and areas from which the fat had been dissolved in preparation. In the connective tissue stroma there were small groups of tumor cells completely surrounded by connective tissue; even solitary cells remained in some areas. Attached to the capsule of the tumor were small portions of seminiferous tubules. Among the tubules were interstitial cells of Leydig, which closely resembled the cells of the tumor, except that their nuclei were not quite as large and prominent.

In a section stained with scarlet red many fine droplets of fat were visible in the cytoplasm of the tumor cells.

Multiple sections of the testis disclosed a few areas of hemorrhage around the site of the tumor but no evidence of extension of the tumor. The seminiferous tubules were uniformly atrophied, and no mature spermatozoa were seen. Most of the tubules were lined with epithelium averaging two cell layers in thickness. The interstitial cells of Leydig were normal in appearance, but their number was less than average.

Case 2.—O. M., a 30 year old Caucasian, was first seen by the Mojave Clinic group, Kingman, Ariz., early in 1940. (The tissue was examined by R. W. H.) The patient complained of enlargement of his breasts and a testicular tumor. His right breast had begun to hypertrophy two and one-half years previously, the left testis one and one-half years before he consulted a physician and the left breast one year before he presented himself. The swollen testis had been painful for over one month.

The patient was well developed and well nourished. The breasts were several times normal size, having a definitely feminine appearance. The right breast was larger than the left. The left testis contained, in the lower pole, a firm, nodular tumor, approximately 2 cm. in diameter. Physical examination revealed no other abnormalities, and roentgenograms contained no indications of metastases. Orchidectomy was performed on the left side.

Fig. 4 (case 3).—Testis with entire parenchyma replaced by nodular tumor. (Size indicated by the metric scale.)

Two and one-half years after the removal of the tumor the patient was well and had gained 30 pounds

13. This feature was pointed out to us by Dr. Newton Evans, Chief Pathologist of the Los Angeles County General Hospital.

(13.6 Kg.). There was no evidence of metastases. The breasts were still enlarged.

Gross Appearance of Specimen.—The testis had a maximum diameter of 3 cm. It contained a nodular tumor, 2 cm. in diameter, surrounded by a fibrous capsule, sharply separating it from the remainder of the testicle (fig. 3). The tumor was firm. It was gray-yellow with a few red areas scattered through its substance.

Microscopic Appearance.—The histologic appearance of the tumor was almost identical with that described in the report of case 1.

CASE 3.—S. P., an 82 year old Caucasian laborer, entered the urologic outpatient department of the Los Angeles County General Hospital Oct. 5, 1936, complaining of a painless swelling of the left testis of two weeks' duration. The past history was normal, except for typhoid fever many years before and an injury of the right hip ten years before. No mention of the testes was made at physical examination in the medical outpatient department one and one-half years earlier.

Physical examination revealed that the left testis was enlarged to two and one-half to three times the normal size, somewhat nodular and slightly tender. The epididymis could not be isolated from the swelling. The right testis was normal to palpation. The following additional abnormalities were found: evidence of a generalized arteriosclerosis; a moderately enlarged prostate gland, and several slightly enlarged, tender left inguinal lymph nodes. The laboratory examination, including roentgenograms, contributed no significant information.

On Oct. 11, 1936, with the patient under spinal anesthesia, orchidectomy on the left side was performed (E. F. N.). Convalescence was uneventful. A Friedman test performed with urine collected two weeks after orchidectomy gave a negative result. The patient did not report for roentgen therapy. He was returned to another department of the hospital for examination a year later by his wife because she believed him to be psychopathic. He had threatened her life and broken into her room several times. The examining physician could find no evidence of insanity. He did not perform a complete physical examination.

The patient was then placed in a rest home under the care of a private physician. Ascites developed, requiring repeated abdominal paracenteses, and the patient died on April 27, 1938, one and one-half years after orchidectomy, at the age of 84.

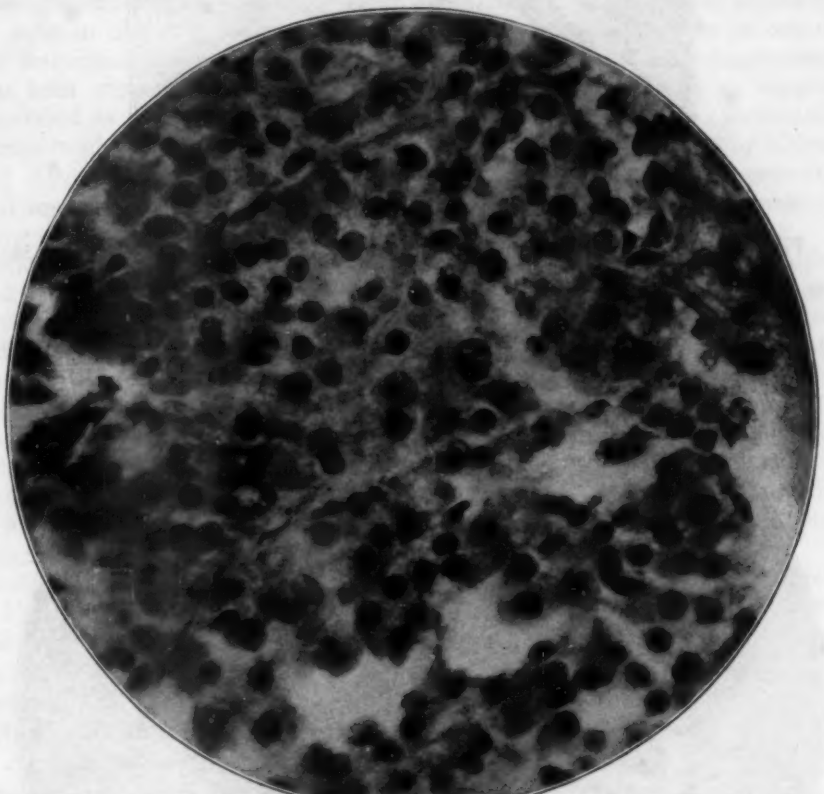


Fig. 5 (case 3).—Area of anaplastic carcinoma showing many mitotic cells. (×450).

Gross Appearance of Specimen.—The specimen consisted of a testicle with the spermatic cord attached. The testicle measured 4 by 3 by 2.5 cm. There were several firm nodules on the external surface at one pole. Sectioning revealed a peculiar, yellow, nodular parenchyma (fig. 4). The nodules were 1 to 2 mm. in diameter and apparently circumscribed by bands of fibrous tissue. No normal testicular tissue was seen.

Microscopic Appearance.—In sections stained with hematoxylin and eosin the tumor was seen to be composed of round to oval groups of tumor cells separated by fairly thick bands of connective tissue. The tumor cells resembled normal interstitial cells. They had

round hyperchromatic nuclei, in which there were many mitotic figures (fig. 5). Nucleoli were prominent and often eccentric. The cytoplasm varied in amount, being rather scanty in some areas and profuse in others. In the latter the liver-like appearance was easily noted. Many granules of almost neutrophilic character were present.

In some areas the tumor cells had invaded the tunica albuginea in small groups or had grown into veins (fig. 6). A few atrophic tubules were seen.

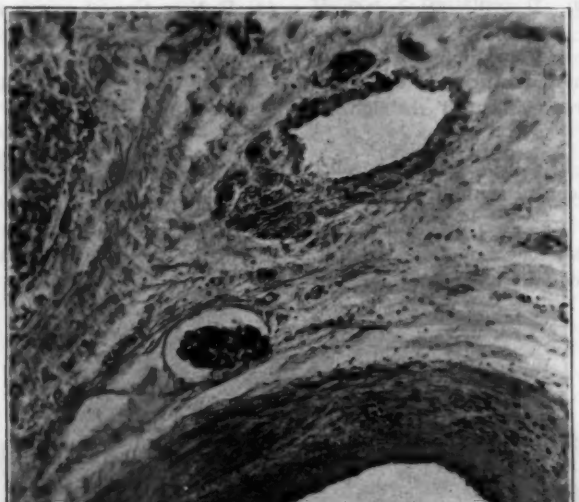


Fig. 6 (case 3).—Section showing growth of tumor cells in a vein. (× 50).

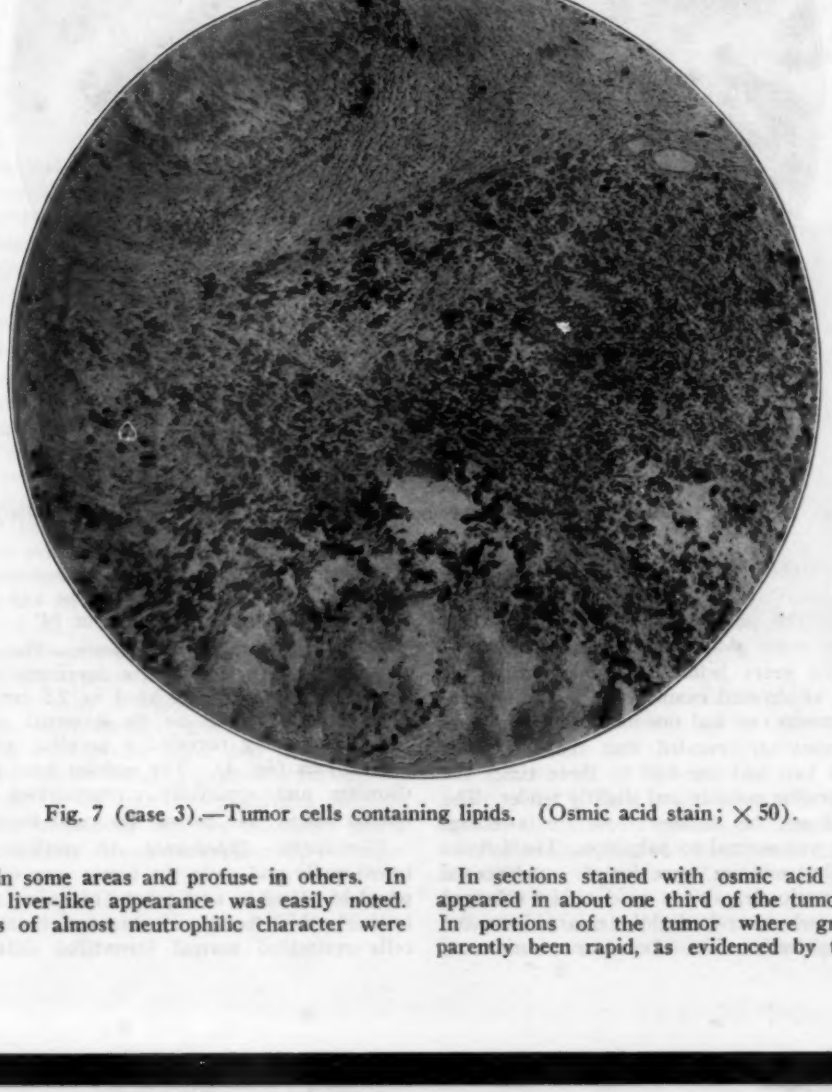


Fig. 7 (case 3).—Tumor cells containing lipids. (Osmic acid stain; × 50).

In sections stained with osmic acid droplets of fat appeared in about one third of the tumor cells (fig. 7). In portions of the tumor where growth had apparently been rapid, as evidenced by the presence of

many mitoses, few or no droplets of fat were seen in the cytoplasm.

COMMENT

Interstitial cell tumors of the testis have two distinctive gross characteristics. First, they are nearly all nodular. This condition is apparent on the external surface and in cross sections of the tumors and is due to the presence of nodules of interstitial cells surrounded by connective tissue. The nodules represent overdevelopment of the normal histologic structure of the groups of interstitial cells. All of the tumors reported here were grossly and microscopically nodular. The tumor reported by Somerford [14] does not appear in the photomicrograph to have this characteristic relation of tumor cells to stroma. The histologic description suggests atopic adrenal tissue. It has been suggested that some of the neoplasms described as of interstitial cell origin are, in fact, tumors of atopic adrenal tissue.

The second distinctive gross characteristic of interstitial cell tumors of the testis is the color. All but 1 of the tumors, including the 3 reported here, were yellow or yellow-brown. The tumor described in the first case reported by Masson [8] was blue-gray. As this was a malignant tumor, the cellular differentiation was perhaps not sufficient to include the formation of cytoplasmic lipids. It is the presence of lipids which causes the characteristic color of interstitial cells, and hence of these tumors. In the malignant tumor reported here (case 3) only the older, more mature parts of the tumor contained lipid (fig. 7).

The microscopic appearance of interstitial cell tumors is unlike that of any other testicular neoplasm. The liver-like cells, with round to slightly oval nuclei and eccentric, punctate nucleoli are without a counterpart. These features characterize the 3 tumors described here and that of Hunt and Budd (table 2), which was available for comparison.

The hormonal changes produced by interstitial cell testicular tumors are interesting. All of the children in whom the tumors have been reported have had precocious bodily and sexual development. These are obviously androgenic phenomena. One would expect endocrine manifestations of the tumors in adults to be on the same basis.

Gynecomastia, which was reported in but 1 of the children, was present in 3 of the adults (15 per cent). Two of these patients had regression of the gynecomastia after removal of the tumor. Evidence has been adduced to indicate that androgens may cause gynecomastia. Selye, McEuen and Collip [15] found development of mammary tissue and lactation in immature male and female rats after the administration of testosterone benzoate, both in the presence and in the absence of the gonads. McCullagh and Rossmiller [16] noted the development of gynecomastia in 6 of 11 men treated for testicular deficiency with methyl testosterone.

The one patient with an interstitial cell tumor on whom hormone assays were performed (Masson [9] and Venning [10]) did not have gynecomastia, despite having the highest level of androgen reported in any condition. Other factors, therefore, must play a part in the development of gynecomastia in some of these patients. The androgen-estrogen ratio [17] may be one of these. The relationship between androgen and inhibin may be another. This has been suggested as a possible explanation of the gynecomastia found in a group of patients reported by Klinefelter, Reifenstein and Albright.[18] The presence of sufficient estrogen to produce gynecomastia has not been demonstrated.

Bonser [19] and Bonser and Robson [20] produced interstitial cell neoplasia, varying from hyperplasia to the formation of malignant tumors, in mice of the Strong A strain by the injection of excessive amounts of various estrogens over a long period. Neither changes in the breasts nor other estrogenic phenomena were produced in most of these mice. The authors ascribe the absence of estrogenic phenomena to the antagonizing effect of the androgen produced by the hyperplastic interstitial cells.

This work suggests the possibility that interstitial cell tumors of the human testis could result from the formation of excessive amounts of estrogen in susceptible persons. If this hypothesis were true, the androgenic changes seen in children with tumors of this type would

14. Somerford, A. E.: A Case of Interstitial Cell Tumor of the Testis in a Boy of Eleven Years, Brit. J. Urol. **13**:13, 1941.

15. Selye, H.; McEuen, C. S., and Collip, J. B.: Effect of Testosterone on the Mammary Gland, Proc. Soc. Exper. Biol. & Med. **34**:201, 1936.

16. McCullagh, E. P., and Rossmiller, H. R.: Methyl Testosterone: I. Androgenic Effects and the Production of Gynecomastia and Oligospermia, J. Clin. Endocrinol. **1**:496, 1941.

17. Glass, S. J., and Bergman, H. C.: Subclinical Adrenogenital Syndrome, Endocrinology **23**:625, 1938.

18. Klinefelter, H. F.; Reifenstein, E. C., Jr., and Albright, F.: Syndrome Characterized by Gynecomastia, Aspermatogenesis Without A-Leydigism, and Increased Excretion of Follicle Stimulating Hormone, J. Clin. Endocrinol. **2**:615, 1942.

19. Bonser, G. M.: Malignant Tumors of the Interstitial Cells of the Testis in Strong A Mice Treated with Triphenylethylene, J. Path. & Bact. **54**:149, 1942.

20. Bonser, G. M., and Robson, J. M.: The Effects of Prolonged Oestrogen Administration upon Male Mice of Various Strains: Development of Testicular Tumors in the Strong A Strain, J. Path. & Bact. **51**:9, 1940.

be due to excessive amounts of androgen produced by these tumors, the cells being capable of the production of larger amounts at this time of life, and the development of gynecomastia (an estrogenic change) in certain adults could be explained by the inability of their interstitial cells to produce enough androgen to antagonize the estrogen. These hypotheses are not in accord with the present understanding of the androgen-estrogen-pituitary balance and do not explain why the gynecomastia in 2 of the adults regressed after the removal of the testicular tumor. However, they indicate the necessity for extensive hormonal studies of patients with interstitial cell tumors of the testis.

The presence of a malignant interstitial cell tumor in a person dying of rapidly growing carcinoma of the prostate, as reported by Sharnoff and Lisa,[12] indicates that estrogen was not present in this patient in sufficient quantity to affect the growth of the prostatic tissue by neutralizing the androgenic effect.

Various other manifestations of these tumors have been described which could be due to excessive amounts of either androgen or estrogen. In several patients the uninvolved testis was small but grew larger after the tumor was removed. Aspermatogenesis, sterility and subnormal libido were present in several patients.

The accompaniment of interstitial cell tumors of the testis with endocrine changes, presumably androgenic, and the high level of 17-keto steroids found by Venning[10] in the urine of a patient with an interstitial cell tumor of the testis are additional evidence that the interstitial cells are the primary source of androgen in the male.

SUMMARY

Twenty-six acceptable interstitial cell tumors of the testis have been reported to date, including 3 new ones reported here. Of this number, 21 were benign and 5 malignant. One of the 3 reported here was malignant and occurred in an 82 year old man. The other 2 were in patients aged 30 and 34 years. One of the patients had gynecomastia which failed to regress after orchidectomy was performed. Each of the 6 children in whom tumors occurred had precocious bodily and sexual development. Three (15 per cent) of the adults had gynecomastia.

Interstitial cell tumors of the testis are usually nodular and yellow or yellow-brown. The microscopic picture is characteristic; there are well circumscribed groups of liver-like cells with rather small, round nuclei and many punctate nucleoli, some of which are eccentric.

It is believed that the manifestations of these tumors offer further proof that the interstitial cells of the testis are the primary source of androgen.

112 North Madison Avenue, Pasadena.

School of Medicine, University of Southern California, Los Angeles.

657 South Westlake Avenue, Los Angeles.